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FEEDING GUIDELINES FOR PREMATURE INFANTS:

EFFICACY AND SAFETY
Doctor of Philosophy (2000)  McMaster University
Clinical Health Sciences (Nursing)  Hamilton, Ontario

TITLE:  Feeding Practice Guidelines for Premature Infants less than 1500 Grams: Efficacy and Safety

AUTHOR:  Shahirose Sadrudin Jamal Esmail Premji, R.N.,  
B.Sc. Biology (McMaster University), B.Sc.N. (McMaster University), M.Sc.N. (University of Toronto)

SUPERVISOR:  J. Fox-Threlkeld, Ph.D.  
Professor  
Faculty of Health Sciences, School of Nursing  
Coordinator  
Clinical Health Sciences (Nursing) Graduate Programme  
McMaster University

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Abstract

Feeding Practice Guidelines for Premature Infants less than 1500 Grams:

Efficacy and Safety

Objectives: To evaluate the efficacy and safety of clinical practice guidelines (CPG) for the nutritional management of very low birth weight infants.

Study Design and Method: A before and after matched cohort study was conducted. During the study periods, 1996/1997 and 1998/1999, data were collected on infants enrolled in the Standard Practice group and CPG group, respectively. CPG were introduced in the neonatal intensive care unit (NICU) in-between these two study periods. Infants < 1500 grams admitted to the NICU who had no major congenital anomalies were enrolled. Data on the first 100 babies who could be matched on birth weight (+/- 100 grams), and gestational age (+/- 1 week) were analyzed.

Results: There was no statistically significant difference between infants in the Standard Practice and CPG groups in: age when feeds were commenced, time to full feeds, the number of feeding interruptions related to feeding intolerance, days on total parenteral nutrition, days to regain birth weight, or days to discharge from hospital. No significant differences were found in the incidence of sepsis and necrotizing enterocolitis, or use of erythromycin. The difference in the use of cisapride was reflective of a change in unit policy rather than the effect of the implementation of CPG.
Conclusions: The findings of this study supported the null hypothesis postulated a priori. Infants may be unresponsive to changes in feeding practices because the state of immaturity of the gastrointestinal system limits the infant’s response to such changes. Inconsistent use of CPG may also explain the findings of this study. A more rigorous study design which includes measurements of relative effectiveness of CPG is needed in order to evaluate the utility of the guidelines, process of care, quality of care, and parent/patient satisfaction.
Acknowledgments

"There is no finer investment
for any community
than putting milk into babies"

Winston Churchill (1943)

I dedicate this dissertation to the Neonatal Community — the premature infants, families of premature infants, nursing staff (especially the CNS/NPs), medical staff, and other care providers (especially Lori the dietitian); my parents, Sadrudin and Nurjehan, and my sister, Rumina, who are my beacons! I am blessed to be a part of this neonatal community and to have such wonderful people in my life — Shukkhar!!
Jo-Ann, Janet, and Stephanie, the dynamic ladies of my thesis committee, I will always be grateful for your devotion to me and this dissertation. Your diversity in educational background, personality, and approach provided an ideal environment for professional and personal growth. This diversity was a source of challenge and strength that enabled me to perform commendably at my oral defense. You are my mentors, especially Janet!

A special thanks to Lori Chessell, Patti Bosher and Lee Wilson. Lori has assisted with data collection, offered guidance, support, and encouragement, provided a shoulder to cry on, and has been a kind, generous and giving friend. Patti spent many hours collecting data and reassuring me that I would meet my self imposed time-lines. Without Lee’s help, with typing revisions, I would not have been able to finish this dissertation in a timely fashion.

Dr. Bosco Paes, Dr. Kevan Jacobson, and Dr. Kyong-Soon Lee, words cannot express my gratitude for the time and energy you have devoted to my professional and personal growth. I would also like to thank Dr. Lee, Dr. Jay Shah and Dr. Salim Daya for their valuable feedback which led to the metamorphosis of the document, which is now the dissertation as it stands today.

Jennifer, Jackie C., Angela, Kathy, Janet, Amanda, Joanne, Marianne and Sharron, otherwise knows as the angels, CNSs, or CNS/NPs, a group of very dynamic
ladies who are not only my colleagues but my friends! I cannot forget Jackie B. who is an ex-CNS/NP. These friends have celebrated good times and, during difficult times, they have provided comfort, support, motivation, strength, and guidance. A special thanks to Jennifer and Jackie C. for their unconditional friendship!

The hard work, patience, pleasant personality, and friendship of everyone mentioned, will always be appreciated and remembered with great fondness. I would also like to extend my appreciation to the Hamilton Health Sciences Corporation Research Development Fund for providing a grant for this research project.

Last but by no means the least, a very special thank you to my parents and sister, without whom none of this would have been possible. This is as much their success as it is mine. For their love, generosity, patience, tolerance, and warmth, I will forever be grateful. I would like to thank my aunts, uncles, and cousins for their caring and nurturing ways during my pursuit of this doctorate. For any errors or omissions in special mentions, my sincere apology!
Table of Contents

Abstract ........................................................................................................... iii

Table of Contents ......................................................................................... viii

List of Tables ............................................................................................... xiii

List of Figures .............................................................................................. xv

List of Appendices ......................................................................................... xvi

Abbreviations Used in Text ........................................................................... xviii

Chapter 1: Introduction, Problem Statement, Objectives, and Hypothesis ...... 1

1.1 Introduction ............................................................................................. 1

1.2 Problem Statement, Purpose and Relevance ........................................... 4

1.3 Objectives and Hypothesis ..................................................................... 4

1.3.1 Objectives ........................................................................................ 4

1.3.2 Hypothesis ....................................................................................... 5

Chapter 2: Biological Basis of Challenges Related to Nutritional Management of

Premature Infants .......................................................................................... 6

2.1 Introduction ............................................................................................ 6

2.2 Coordinated Sucking and Swallowing Reflex ......................................... 7

2.3 Esophageal Motility .............................................................................. 11

2.4 Development of Stomach .................................................................... 12
2.4.1 Gastric digestion (excluding intrinsic factor) ........................................ 15
2.4.2 Gastric emptying .................................................................................. 16
2.5 Intestinal Transit ..................................................................................... 18
2.6 Summary .................................................................................................. 19

Chapter 3: Nutritional Management: Current Knowledge, Standard Practice and Development of Clinical Practice Guidelines ........................................ 21
3.1 Literature Search Strategy ..................................................................... 21
3.2 Literature Review .................................................................................. 23
  3.2.1 Timing of feeding .............................................................................. 23
  3.2.2 Feeding during indomethacin therapy for PDA closure .................... 37
  3.2.3 Route of feeding .............................................................................. 39
  3.2.4 Type of feed ...................................................................................... 53
  3.2.5 Feeding advancement ..................................................................... 59
  3.2.6 Feeding intolerance: definition and management ......................... 68
  3.2.7 Nursing management of enteral tube feedings .............................. 75
3.3 Conclusion ............................................................................................. 78

Chapter 4: Clinical Practice Guidelines ...................................................... 79
4.1 Introduction ............................................................................................ 79
4.2 Development of Guidelines .................................................................. 80
4.2.1 Consensus decision-making process ........................................ 80

Chapter 5: Methodology ................................................................. 89

5.1 Introduction ............................................................................ 89

5.2 Dissemination, Diffusion and Implementation of CPG .................. 89

5.2.1 Dissemination ..................................................................... 89

5.2.2 Roger’s theory of diffusion: conceptual framework for adoption or
    rejection of CPG .................................................................... 93

5.2.2.1 stages in the innovation-decision process ......................... 93

5.2.2.2 perceived attributes of innovations .................................. 96

5.2.2.3 diffusion: components and as a social process ................ 99

5.2.3 Implementation of CPG ....................................................... 104

5.2.4 Critical appraisal of theory, research and recommendations .... 108

5.3 Setting .................................................................................... 110

5.4 Design: Strengths and Limitations .......................................... 111

5.5 Inclusion and Exclusion Criteria ............................................. 111

5.6 Data Collection ....................................................................... 113

5.7 Sample Size Justification ........................................................ 114

5.8 Statistical Analysis .................................................................. 115

5.9 Plan for Protection of Subject’s Rights ..................................... 117
5.9.1 Informed consent/risks and benefits ........................................... 117
5.9.2 Confidentiality ......................................................................... 118
5.9.3 Dissemination of results ............................................................ 118

Chapter 6: Results ............................................................................ 119
6.1 Introduction .................................................................................. 119
6.2 Demographic and Clinical Characteristics .................................... 119
6.2.1 Study environment .................................................................. 119
6.2.2 Eligible population ................................................................. 121
6.3 Descriptive Statistics of Study Participants ................................... 126
6.4 Research Findings As They Relate To The Research Question ...... 129
6.4.1 Age when feeds were commenced ....................................... 129
6.4.2 Time (days) to full feeds ......................................................... 131
6.4.3 Feeding interruptions related to feeding intolerance .............. 133
6.4.4 Days on TPN ........................................................................... 135
6.4.5 Days to regain birth weight .................................................... 136
6.4.6 Days to discharge from hospital .......................................... 137
6.4.7 Incidence of sepsis ................................................................. 137
6.4.8 Incidence of NEC ................................................................. 139
6.4.9 Use of prokinetic agents ......................................................... 139
Chapter 7: Discussion ............................................. 140
7.1 Introduction .................................................. 140
7.2 Extrauterine Environmental Factors ..................... 141
7.3 Intrauterine Environmental Factors ..................... 147
7.4 Compliance with CPG ....................................... 155
7.5 Relationship Between Confounders and Study Outcomes ............................................. 159
7.6 Study Implications .......................................... 161
  7.6.1 Practice implications .................................. 161
  7.6.2 Policy implications .................................... 162
  7.6.3 Implications for future research ..................... 163
7.7 Conclusion .................................................. 165
References ......................................................... 167
List of Tables

Table 1. Ontogeny of Coordinated Sucking and Swallowing Reflex and Esophagus ........................................... 9

Table 2. Ontogeny of Stomach by Week of Gestation (Part 1 - 4 to 20 weeks) ............................................. 13

Table 3. Ontogeny of Stomach and Intestinal Transit by Week of Gestation (Part 2 - 21 to 40 weeks) .................................................. 14

Table 4. Pilot Study Data for Timing (in days) of Feeding ........................................................................ 25

Table 5. Characteristics of Studies on Minimal Enteral Feeding ................................................................. 26

Table 6. Characteristics of Studies on Continuous Versus Intermittent Bolus Gavage Feeding Method ................................................................. 44

Table 7. Characteristics of Studies on Slow Versus Rapid Advances in Feeds ................................................ 62

Table 8. Feeding Practice Guidelines for Infants in the < 750 grams Category ............................................. 82

Table 9. Feeding Practice Guidelines for Infants in the ≥ 750 grams and < 1000 grams Category ................................. 83

Table 10. Feeding Practice Guidelines for Infants ≥ 1000 grams and < 1500 grams Category ......................... 84

Table 11. Comparison of Maternal and Mode of Delivery Characteristics in the Study Groups ........................................ 127

Table 12. Comparison of Infant Characteristics in the Study Groups ........................................................... 128

Table 13. Comparison of Groups on Major Study Outcomes ........................................................................... 132

xiii
Table 14. Sepsis: Number of Positive Blood Cultures and Organism(s) Isolated by Study

Group .............................................................. 138
List of Figures

Figure 1. Parameters for nurses to follow for decision regarding management of gastric aspirates and holding feeds ............................................. 86

Figure 2. Strategies directed at nursing staff aimed at dissemination, diffusion, and implementation of CPG ......................................................... 90

Figure 3. Five stages in the innovation-decision process ......................................................... 94

Figure 4. Flow diagram of study design ................................................................................. 112

Figure 5. Flow chart of infants admitted to the NICU and included in the Standard Practice group ........................................................................... 123

Figure 6. Flow chart of infants admitted to the NICU and included in the CPG group ........ 125

Figure 7. Boxplot of age when feeds were commenced in the Standard Practice group and CPG group ................................................................. 130

Figure 8. Boxplot of number (in days) of feeding interruptions related to feeding intolerance in the Standard Practice group and the CPG group .............. 134
List of Appendices


Appendix C: Modified Bell Staging Criteria For Necrotizing Enterocolitis

Appendix D: Classification of Intrauterine Growth Restriction

Appendix E: Record Form For Data Collection Related to Maternal History, Mode of Delivery, and Infant Characteristics

xvi
Appendix F: Record Form For Data Collection of Variables Related to Feeding

Appendix G: Ethical Approval
Abbreviations Used in Text

AA  arachidonic acid
CINAHL  Cumulative Index of Nursing in Allied Health Literature
CNS/NP  clinical nurse specialist/neonatal practitioner
CPG  clinical practice guidelines
DHA  docosahexanoic acid
EGF  epidermal growth factor
IUGR  intrauterine growth restriction
LES  lower esophageal sphincter
MEN  minimal enteral nutrition
MeSH  medical subject headings
MMC  migrating motor complex
NEC  necrotizing enterocolitis
NGMRGB  neonatal gastrointestinal motility research group
NICU  neonatal intensive care unit
NNS  non-nutritive sucking
PDA  patent ductus arteriosus
pH  hydrogen ion concentration

... cont’d

Abbreviations which appear in tables and figures are explained and located in the corresponding legend.
Abbreviations Used in Text ... cont’d

RDS           respiratory distress syndrome
TIPP          trial of indomethacin prophylaxis in premature infants
TPN           total parenteral nutrition
VLBW          very low birth weight infants

Abbreviations which appear in tables and figures are explained and located in the corresponding legend.
Chapter 1

Introduction, Problem Statement, Objectives, and Hypothesis

1.1 Introduction

The survival rates of very low birth weight (VLBW) infants, those < 1500 grams, have improved over the years (Hack et al., 1995; Robertson, Hrynchysyn, Etches, & Pain, 1992; Saigal, Rosenbaum, Stoskopf, & Sinclair, 1984; Wojtulewicz et al., 1993). In Hamilton-Wentworth County, the study setting, Saigal et al. (1984) compared survival of infants 501 to 1000 grams born between 1973 to 1976 and 1977 to 1980, and found an increase from 24% to 49% in birth rate between these 2 cohorts. Similar findings have been reported in more recent population-based studies conducted in Canada (Robertson et al., 1992), the United States (Hack et al., 1995; Hack, Friedman, & Fanaroff, 1996), and Australia (The Victorian Infant Collaborative Study Group, 1997). When comparing 1-year survival of infants 500 to 1250 grams for 1978 to 1979 and 1988 to 1989, Robertson et al. (1992) report an increase from 36% to 67%. Infants weighing <750 grams have had the largest recent improvement in survival (Hack et al., 1991; Hack et al., 1995; Hack et al., 1996). The overall survival increases with increasing birth weight (Hack et al., 1991; Hack et al., 1995; Saigal et al., 1984; Robertson et al., 1992) and increasing postnatal age (Cooper, Berseth, Adams, & Weisman, 1998).

The improved survival of VLBW infants may be the result of increasing knowledge
regarding the development of the respiratory tract. The use of assisted ventilation in the delivery room and use of surfactant for the treatment of hyaline membrane disease may account for this improved survival (Hack & Fanaroff, 1999). Other factors, such as, changes in obstetrical management (Joseph et al., 1998), use of antenatal steroids (NIH Consensus Conference, 1995; Hack et al., 1995), and regionalization of perinatal care (Delaney-Black et al., 1989; Verloove-Vanhorick, Verwey, Ebeling, Brand, & Ruys, 1988), may also contribute to improved survival rates.

VLBW infants have unique compositional characteristics as their bodies are primarily water, and endogenous nutritional stores are limited (1% fat and 8.5% protein) (Buus-Frank & Adams, 1994). These endogenous nutritional stores are quickly depleted under conditions of starvation (4.5 days under total starvation versus 7 days with intravenous glucose infusions) (Adamkin, 1986). VLBW infants also have high metabolic needs (Heird, 1983, 1987). The unique compositional and metabolic characteristics make it imperative that these infants receive early nutrition to ensure their continued survival (Buus-Frank & Adams, 1994; Heird, 1983, 1987). According to Lucas (1990), there is preliminary evidence to suggest that nutritional management of premature infants in the early weeks of life has an impact on later growth and development. This concept is referred to as programming (Lucas, 1990), and there is compelling evidence in animal studies, including primates, that a stimulus (early nutrition or malnutrition) during a brief critical or sensitive period of development, may have life-long consequences (Lucas, 1990; Morley & Lucas, 1993). Early nutritional management may have long-term implications
for growth (weight, stature, and fat stores), neurological development (brain size, brain cell number, and performance) and health (atherosclerosis, and allergies) (Lucas, 1990; Morley & Lucas, 1993; Steer, Lucas, & Sinclair, 1992).

Providing nutritional support to the increasing number of VLBW infant survivors has been a major challenge for a number of reasons: (a) lack of knowledge about when and how to feed premature infants; (b) limited clinical experience; and (c) wide variation in practice (Kelly & Newell, 1994). As well, hormonal, anatomic, and functional limitations of VLBW infants, and the additive effect of critical illness, complicate feeding decisions in this population of infants. Wide variation in feeding practice has been demonstrated for infants < 1500 grams in a pilot study conducted in a 33 bed, university-affiliated teaching hospital, neonatal intensive care unit (NICU) (Premji, Chessell, Paes, Pinelli, & Jacobson, 1999, unpublished data, see Appendix A). The study examined feeding practices such as timing of first feeding, feeding orders, volume and frequency of feed increases, and whether orders were actually implemented. These variations in practice are thought to explain the differences noted in the outcome of days to full feeds.

Clinical practice guidelines (CPG) are one strategy to address the challenges of feeding VLBW infants as they are evidence-based, hence, limit inappropriate variation in practice (Lewis, 1995). CPG attempt to “refine decision making and to narrow practice variation to a degree unlikely to be achieved ‘naturally’ by the target audience(s).” (Lewis, 1995, p. 1074). Additionally, the guidelines will assist practitioners with limited clinical experience to make decisions about appropriate care for nutritional management of
VLBW infants. Adoption of CPG has consequences for VLBW infants. Guidelines should improve the nutritional, neurological development and health outcomes of VLBW infants. There is little evidence about the effectiveness of CPG in a NICU setting, therefore, evaluation of the implementation of such a clinical policy is needed.

1.2 Problem Statement, Purpose and Relevance

CPG should provide an optimal feeding regimen which maintains gut function and integrity, thereby decreasing gastrointestinal pathology such as feeding intolerance and decrease adverse effects such as necrotizing enterocolitis (NEC). The purpose of this study was to evaluate the efficacy and safety of CPG for the nutritional management of VLBW infants. It is hoped that this type of regimen will improve patient outcomes, be cost effective to the health care system, and increase parent’s satisfaction of care provided to their infant. CPG will allow clinicians to take a evidence-based approach to decision-making, standardize their practice, and eliminate personal bias in the nutritional management of VLBW infants. This study will contribute knowledge to the area of nutritional management of premature infants < 1500 grams.

1.3 Objectives and Hypothesis

1.3.1 Objectives

1. To measure age when feeds were commenced in order to determine compliance with implementation of CPG.

2. To measure primary outcome of days to full feeds, and other end points of feeding intolerance including number of feeding interruptions, and days on total parenteral
nutrition (TPN), before and after the implementation of CPG, to determine if CPG promote feeding tolerance.

3. To measure secondary outcomes of days to regain birth weight and age at discharge, to determine if CPG improve weight gain and allow earlier discharge.

4. To monitor for adverse effects, such as NEC and sepsis, before and after the implementation of CPG to determine if CPG are safe.

5. To monitor the use of prokinetic agents, such as erythromycin and cisapride, for the management of feeding intolerance to ensure that differences in outcomes of this study, if any, are related to the use of CPG and not the use of prokinetic agents.

1.3.2 Hypothesis

The null hypothesis is as follows: there will be no significant difference between infants in the CPG group and infants in the Standard Practice group in:

1. Age when feeds were commenced.

2. Time (days) to full feeds.

3. Number of feeding interruptions related to feeding intolerance.

4. Days on TPN.

5. Days to regain birth weight.

6. Days to discharge from hospital.

7. Incidence of sepsis.

8. Incidence of NEC.

9. Use of prokinetic agents such as erythromycin and cisapride.
Chapter 2

Biological Basis of Challenges Related to Nutritional Management of

Premature Infants

2.1 Introduction

An understanding of gastrointestinal ontogeny will form the basis for the establishment of optimal feeding management guidelines by developing practices which take into consideration the structural and functional maturity of the gastrointestinal system. An understanding of gastrointestinal ontogeny will ensure that the CPG developed for premature infants < 1500 grams maintain gut function and gut integrity, as well as decrease such gastrointestinal pathologies as NEC. Additionally, it is hoped that current knowledge into the natural history of gastrointestinal ontogeny will contribute to the body of knowledge regarding the nutritional management of VLBW infants, and prompt research in this area.

Current knowledge of gastrointestinal ontogeny focuses on the effects of the intrauterine and extrauterine environment upon that process. A comprehensive overview of the ontogeny of the gastrointestinal system, written by the author, has been included in Appendix B. For the purposes of this discourse, only those aspects important to the development of CPG will be presented. The following discussion will focus on the ontogeny of: (a) coordinated sucking and swallowing reflex; (b) esophageal motility; (c)
stomach, including gastric digestion, gastric emptying; and (d) intestinal transit. Chapter 3 will elucidate the application of this knowledge to the development of CPG.

2.2 Coordinated Sucking and Swallowing Reflex

Effective sucking behavior is a prerequisite for safe and effective oral feeding, and implies that an infant has achieved neurologic, behavioral, and physiologic maturity (Medoff-Copper & Ray, 1995; Medoff-Copper, Verklan, & Carlson, 1993). Sucking behaviors have been classified into two modes, namely, nutritive and non-nutritive sucking (NNS), based on sucking patterns (Wolff, 1972). Nutritive sucking has a continuous rhythmic pattern which consists of slower mean rates of sucking, usually about half that of NNS, with shorter periods of pauses. Nutritive sucking occurs solely in the presence of oral fluid (Herbst, 1983). Nutritive sucking and swallowing are not fully developed until approximately 34 weeks gestational age (Dumont & Rudolph, 1994). Gestational age at birth and exposure to enteral feeds do not influence the development of the mechanism of nutritive sucking and swallowing (Kelly & Newell, 1994).

NNS alternates between unpredictable bursts of activity and rest periods in the absence of oral fluid intake such as amniotic fluid or milk, and is characterized by a rapid rate of sucking, approximately 2 or more sucks per second (Herbst, 1983). NNS develops before nutritive sucking, and in its most immature form consists of only mouthing movements (Herbst, 1983). The development of NNS and related factors, for example infant state, have been described in detail in a review conducted by the author and Dr. Paes (2000) (see Appendix B). NNS could not be recommended as an effective
intervention for the promotion of gastrointestinal function and growth in premature infants based on the randomized control trials and meta analyses appraised in this review.

Swallowing requires the coordination of a number of activities including movement of milk back into the pharynx, protection of the airway, inhibition of breathing, sequential contractions of the esophagus, relaxation and contraction of the lower esophageal sphincter (LES) and gastric fundus (Newell, 1996; Davenport, 1984). Table 1 outlines the ontogeny of coordinated sucking and swallowing by week of gestation. From 12 to 16 weeks the first signs of swallowing are seen in the fetus. The fetus initially swallows small amounts of amniotic fluid (2 to 7 ml per day) and the volume increases with increasing gestational age. In contrast, a fetus at term gestational age swallows approximately 300 to 700 ml per day (Pritchard, 1966). It has been postulated that amniotic fluid: (a) may play a role in providing luminal nutrients as it contains proteins (Pritchard, 1966), carbohydrates, and triglycerides (Kelly & Newell, 1994); (b) provides volume which stimulates the secretion of enteric hormone, thereby, promoting maturation of motility (Kelly & Newell, 1994); and (c) contains large amount of growth factors (Weaver & Walker, 1988; Kelly, Newell, Brownlee, & Primrose, 1994) which may play a role in the growth and differentiation of infant tissues (Read et al., 1984).

In amniotic fluid, epidermal growth factor (EGF), a small polypeptide, increases with increasing gestational age (Kelly et al., 1994). EGF may play a role in growth and maturation of the small intestine (Kelly et al., 1994; Read et al., 1984). In laboratory studies, EGF binds to the EGF receptors and accelerates tissue maturation. Additionally,
### Table 1. Ontogeny of Coordinated Sucking and Swallowing Reflex and Esophagus

<table>
<thead>
<tr>
<th>Development</th>
<th>What Appears and When it Appears</th>
<th>Nutritive sucking</th>
<th>fully developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordinated sucking and swallowing reflex</td>
<td>First sign of swallowing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Esophagus</th>
<th>Appears as distinct structure</th>
<th>Increase in thickness of muscle layers</th>
<th>Peak in density of neurons and number of ganglion cells and nerve fibres in myenteric plexus</th>
<th>Decline in neuron density</th>
<th>Decline in number of ganglion cells and nerve fibres, then number constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circular muscle and neurons evident</td>
<td>Circular muscle and neurons evident</td>
<td>Increase in thickness of muscle layers</td>
<td>Peak in density of neurons and number of ganglion cells and nerve fibres in myenteric plexus</td>
<td>Decline in neuron density</td>
<td>Decline in number of ganglion cells and nerve fibres, then number constant</td>
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<td></td>
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</tr>
</tbody>
</table>

Pattern of expression of hormones and peptides similar to newborn

| | Upper ES function detected; motility not coordi-nated |
| | High pressure zone in LES Increase LES pressure |

Abbreviations: esophageal sphincter (ES); lower esophageal sphincter (LES)


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EGF stimulates deoxyribonucleic acid and protein synthesis. These actions of EGF may facilitate adaptation from intrauterine to extrauterine nutrition (Weaver & Walker, 1988).

In animal studies, when saline was substituted for amniotic fluid, gut hypoplasia resulted (Newell, 1996). As well, fetal swallowing defects in animal models have shown associated abnormalities of the gastrointestinal system and failure of growth of the gastrointestinal system (Trahair & Harding, 1992, 1995; Montgomery, Mulberg, & Grand, 1999). Human infants with esophageal atresia do not have associated functional problems of the gastrointestinal system once the lesion is corrected. The significance of growth factors in the growth and differentiation of the gastrointestinal system needs to be further studied (Foglia, 1994; Montgomery et al., 1999).

For VLBW infants, lack of enteral stimuli may be considered unphysiologic (Lucas, 1993b) as there is no longer a regulatory influence on the development of the gastrointestinal system. After birth, the only source of trophic factor is milk (Read et al., 1984). Enteral nutrition may be important in maintaining mucosal morphology and, therefore, the functional characteristics of the gastrointestinal tract in VLBW infants (Sharma, Schumacher, Ronaasen, & Coates, 1995). Atrophic changes in the gastrointestinal system, such as decreased weight of the intestine, pancreas and stomach, are associated with withholding enteral feeds (Lucas, Bloom, & Aynsley-Green, 1983). On the other hand, feeding can lead to deleterious outcomes, for instance, NEC. In 90% to 95% of cases, NEC occurs in babies who have been fed (Kliegman & Fanaroff, 1981; Stoll, Kanto, Glass, Nahmias, & Brann, 1980). Whether feeding infants is a coincidental
or contributing factor in the development of NEC remains to be established (Stoll et al., 1980). The cause of NEC is not completely understood (Rayyis, Ambalavanan, Wright, & Carlo, 1999) as many factors, including rapid feeding advancement, have been associated with an increased incidence of NEC (Anderson & Kliegman, 1991; Kliegman & Fanaroff, 1984; McKeown et al., 1992; Zabielski, Groh-Wargo, & Moore, 1989).

2.3 Esophageal Motility

The esophagus appears as a distinct structure at 4 weeks and elongates rapidly as development progresses (Grand, Watkins, & Torti, 1976; Montgomery et al., 1999). Table 1 outlines the ontogeny of the esophagus by week of gestation. At 8 weeks gestation circular muscle and neurons are evident in the esophagus. It is not until 13 weeks gestation that the longitudinal muscle appears. The muscle layer increases in thickness with increasing gestational age until term, after which, the growth is slower (Hitchcock, Pemble, Bishop, Spitz, & Polak, 1992a; Montgomery et al., 1999). At 16 to 20 weeks gestation there is a peak in density of neurons, and in number of ganglion cells and nerve fibers in the myenteric plexus, after which time there is a rapid decrease. The decline in neuron density continues until infancy when adult levels are reached. In contrast, the number of ganglion cells and nerve fibers in the myenteric plexus decrease until 30 weeks gestation, after which the number remains constant even though the esophagus continues to grow (Hitchcock et al., 1992a; Montgomery et al., 1999). By 22 weeks gestation patterns of expression of hormones and peptides similar to newborns and infants are seen (Hitchcock, Pemble, Bishop, Spitz, & Polak, 1992b; Montgomery et al.,

At 32 weeks gestation, upper esophageal sphincter function is detected. At this time, esophageal motility is not coordinated and the motor activity is similar to that seen in older children with gastro-esophageal reflux and dismotility. Both postnatal age and milk feeds promote maturity of esophageal motor activity (Gryboski, 1965). Acid reflux is prevented by a number of barrier mechanisms. The lower esophageal sphincter (LES) pressure is one such barrier mechanism. In order to provide a barrier against reflux of stomach contents into the esophagus, the LES pressure must be higher than the fundal pressure (Newell, 1988). Studies have shown that at 26 weeks there is a high pressure zone in the LES. Effective sphincter pressure to prevent reflux, however, increases with gestational age at birth. A 28 week gestation infant has a less effective sphincter pressure (effective LES of 4 mmHg) compared to a term infant (effective LES 18 mmHg) (Newell, Sarkar, Durbin, Booth, & McNeish, 1988). Maturation of the sphincter is not influenced by gestation at birth but it directly related to postconceptional age. The sphincter pressure rises with increasing postconceptional age (Newell et al., 1988).

2.4 Development of Stomach

The stomach develops at about 4 weeks gestation (Arey, 1974; Newell, 1996). Table 2 and Table 3 delineate the ontogeny of the stomach by week of gestation. By approximately 20 weeks gestation, the macroscopic and microscopic appearance of the
Table 3. Ontogeny of Stomach and Intestinal Transit by Week of Gestation (Part 2 - 21 to 40 weeks)

<table>
<thead>
<tr>
<th>Development</th>
<th>21 weeks</th>
<th>23 weeks</th>
<th>24 weeks</th>
<th>25 weeks</th>
<th>26 weeks</th>
<th>28 weeks</th>
<th>29 weeks</th>
<th>30 weeks</th>
<th>31 weeks</th>
<th>32 weeks</th>
<th>33 weeks</th>
<th>35 weeks</th>
<th>36 weeks</th>
<th>38 weeks</th>
<th>40 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Gastric digestion | Lipolytic activity | Secrete gastric acid, pH decreases with increasing GA | | | | | | | | | | | | | |<--- Peak lipolytic activity ----> <---------- Decrease in lipolytic activity --------------->
| Gastric emptying | Increase in thickness of muscle layers in stomach | | | | | | | | | | | | | | |<--- Increase in temporal association of antral and duodenal contractions --------------->
| | Intraluminal contraction | pressure | amplitudes | approach | term value | | | | | | | | | | | |<--- Increase in number and amplitude ----> |<--- of duodenal contractions --------------->
| Minimal evidence of transit through the gut | | | | | | | | | | | | | | | |<--- Four fold increase in amplitude of gastric Antral contractions --------------->
| Antral and duodenal activity | | | | | | | | | | | | | | | |<--- MMC appears; poorly formed and disorganized | MMC becomes more organized --------------->
| Intestinal transit | MMC becomes more organized | Motlin receptor | | | | | | | | | | | | | | |<--- MMC becomes more organized --------------->

Abbreviations: gestational age (GA); migrating motor complex (MMC)

Table 2. Ontogeny of Stomach by Week of Gestations (Part 1 - 4 to 20 weeks)

<table>
<thead>
<tr>
<th>Development</th>
<th>What Appears and When it Appears</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td>Stomach</td>
<td>Stomach develops</td>
</tr>
<tr>
<td>Gastric digestion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circular muscle layers</td>
</tr>
</tbody>
</table>

<----------------------------------------------------------------------->  Minimal evidence of transit through gut  <----------------------------------------------------------------------->

stomach is similar to that of the term infant (Kelly & Newell, 1994).

2.4.1 Gastric digestion (excluding intrinsic factor)

Both acid and pepsin are important for digestion. Gastric acid activates pepsinogen to form pepsin, an enzyme necessary for cleaving protein molecules (Rhoades & Tanner, 1995). Peptic activity has been shown in the stomach of VLBW infants (Adamson, Esangbedo, Okolo, & Omene, 1988). Although hydrochloric acid has been found in the fetal stomach from 19 weeks gestation (Lucas-Keene & Hewer, 1929) it is not known how much acid the fetus produces in utero (Kelly, Newell, Brownlee, Primrose, & Dear, 1993). Kelly et al. (1993) have demonstrated that premature infants, 24 to 29 weeks gestation, are able to secrete gastric acid but the intragastric acid-base balance (pH) decreases with increasing gestational age (3.7, 2.5 and 1.8 for infants of 24 to 25, 26 to 27 and 28 to 29 weeks' gestation, respectively). By the third week of life, all infants, irrespective of gestational age at birth, are able to maintain a gastric pH below 2. Thus, with increasing postnatal life, lower gestational age infants secrete more acid. No evidence of diurnal rhythm was found in pH recordings of these VLBW infants (Kelly et al., 1993). The consequence of the absence of such a rhythm in VLBW infants is unknown, however, it may represent a stage of development, that is, rhythm develops with increasing gestational age.

From 11 weeks gestation, the fundal region of the stomach secretes gastric lipase (acid stable) which is important in the initial hydrolysis of dietary triglycerides. Lipolytic activity is present in infants as young as 23 weeks gestation. Peak lipolytic activity in
gastric aspirates have been demonstrated at 30 to 32 weeks gestation, after which time, lipolytic activity decreases again until term gestation. Changes in lipolytic activity at different gestational ages may represent the actual developmental profile of lipolytic activity. It has been postulated that peak levels at 30 to 32 weeks gestation represent a combination of lingual and gastric lipase. Lipase in the lingual gland begins to disappear with increasing gestational age. In adults, gastric lipase predominates and there is a reduction in total lipase content in the stomach. Comparisons of lipolytic activity profiles of infants born at different gestational ages and infants at different postconceptional age, show similar patterns, suggesting that the environment (i.e., exposure to multiple drugs) has little effect on the developmental profile of lipolytic activity which is essential for normal fat digestion (Lee, Borysewicz, Struve, Raab, & Werlin, 1993).

2.4.2 Gastric emptying

The gastrointestinal tract has a muscle coat consisting of two layers, the inner circular layer and the outer longitudinal layer. Early in gestation, layers of smooth muscle develop, in a craniocaudal pattern, in the mesenchymal layer surrounding the bowel lumen. The circular muscle layers develop before the longitudinal muscle layers. During the 5th week of gestation the circular muscle layers of the stomach become recognizable, but it is not until 8 weeks gestation, that the longitudinal muscle layers appear (Dumont & Rudolph, 1994). Each muscle layer increases in thickness with increasing gestational and postnatal age. At 25 weeks gestation the intraluminal contraction pressure amplitudes approach 60% of the values noted at term (Berseth, 1989).
Although swallowing is first observed at 12 to 16 weeks gestation there is minimal evidence of transit through the gut before 30 weeks gestation (Gupta & Brans, 1978). Intact coordinated motor activity of the fundus, antrum, pylorus, and duodenum are important for effective gastric emptying (Berseth, 1996). In adults, when milk enters the stomach passive accommodation of the volume occurs. Initially, antral contractions cease and duodenal contractions increase. Later, the antrum, pylorus, and duodenum contract in a coordinated fashion to empty the liquid from the stomach. Alteration in the coordination of motor activity in these areas can result in delayed gastric emptying (Berseth, 1996; Houghton et al., 1988).

The pattern of gastric emptying varies for liquids and solids. Liquid meals empty in a curvilinear fashion with rapid emptying that then diminishes with time. The rate of liquid gastric emptying is dependent on the volume of the meal in the stomach. Gastric emptying of solid meals is controlled by the distal stomach which prevents the passage of any particle > 2 mm. The pattern of gastric emptying of solid meals is predominantly linear (Dumont & Rudolph, 1994).

Gastric emptying is slower in premature infants (Siegel, 1983). The amplitude of the gastric antral contractions increases with increasing gestational age with a 4-fold increase noted between 28 and 38 weeks gestation (10 mmHg and 40 mmHg respectively) (Bisset, Watt, Rivers, & Milla, 1988). Between 29 and 32 weeks gestation, the number and amplitude of duodenal contractions increase markedly (Milla & Fenton, 1983). In premature infants 25 to 35 weeks gestation, antral activity is not always associated with
duodenal activity. The association of antral activity with duodenal activity was 5 times lower in premature infants than in term infants. With increasing gestational age, the percentage of antral activity with duodenal activity was significantly higher and appeared to be correlated with changes in duodenal motor activity. The lack of antroduodenal coordination in premature infants has been implicated in delayed gastric emptying (Ittmann, Amarnath, & Berseth, 1992). In addition, premature infants demonstrate poorly organized and non-rhythmic gastric pressure waves (Gryboski, 1965).

2.5 Intestinal Transit

The ontogeny of the intestine is summarized, by week of gestation, in Table 3. In adults, two types of intestinal motor patterns are observed. The fed response is the first type of pattern seen when food is ingested. At multiple levels of the intestine, there are simultaneous sporadic repetitive contractions of variable amplitudes which result in the mixing and churning of nutrients with gastric secretions. As well, nutrients are repeatedly presented to the mucosal surface. The second type of pattern is seen during fasting when the intestine becomes relatively quiet and contractions disappear (Berseth, 1996). This type of pattern consists of three consecutive phases. Phase I, referred to as the silent phase or motor quiescence, has no contractile activity. Phase II is marked by irregular contractions and is immediately followed by phase III which consists of regular phasic contractions. The cycle repeats with phase I occurring after phase III; the 3 phases occur every 60 to 90 minutes. Phases II and III travel slowly down the intestine and this behavioral pattern is called the migrating motor complex (MMC) (Rhoades & Tanner,
1995). The MMC is responsible for moving the nutrients forward and is considered to be the "intestinal housekeeper" (Berseth, 1996, p. 180). Although the MMC appears between 32 and 35 weeks gestational age, it is poorly formed and shows disorganized, random bursts of motor activity (Bisset, Watt, Rivers, & Milla, 1988). As well, "the intervals between complexes, amplitude of contractions, velocity of migration along the bowel, and reliability of propagation are less than in the adult" (Dumont & Rudolph, 1994, p. 664).

The MMC is under hormonal control. In adults, there is a sinusoidal cycle of the hormone motilin. A concurrent increase in plasma motilin level is observed with the initiation of MMC. In premature infants two aspects of hormonal regulation of the MMC are absent. First, a functional antral smooth muscle motilin receptor is not present until 32 weeks gestation. Second, there is no cyclic release of motilin (Berseth, 1996). Cord blood has a low concentration of circulating motilin. At birth there is a 10 fold increase with peak levels reached at approximately 2 weeks postnatal life (Lucas, Bloom, & Aynsley-Green, 1982).

2.6 Summary

One can, therefore, surmise that efficient sucking and swallowing develop at approximately 32 to 34 weeks gestation, and gastric emptying and intestinal propulsive activity matures after 30 weeks gestation (Dumont & Rudolph, 1994). Neuromuscular development occurs early in gestation, however, normal patterns of contractile activity do not occur until after birth. By approximately 34 to 35 weeks gestational age the
the gastrointestinal system is capable of effective digestion of enteral nutrients. Furthermore, the gastrointestinal system is capable of moving these nutrients forward through the gastrointestinal tract. Consequently, infants born at 34 to 35 weeks gestation have a structurally and functionally mature foregut, and intact neuromuscular function to tolerate enteral feeds without medical intervention. The nutritional management of infants born before 34 to 35 weeks gestation requires an awareness of the natural history of gastrointestinal ontogeny, particularly the effects of the intrauterine and extrauterine environment upon coordinated sucking and swallowing reflex, esophageal motility, gastric digestion, gastric emptying, and intestinal transit. Additionally, decisions related to feeding VLBW infants should be based on current research. Chapter 3 applies this present understanding of gastrointestinal ontogeny in the development of CPG for premature infants < 1500 grams by probing various areas of nutritional management.
Chapter 3

Nutritional Management: Current Knowledge, Standard Practice and Development of Clinical Practice Guidelines

3.1 Literature Search Strategy

Attempts to ascertain CPG, for the nutritional management of infants < 1500 grams that were research based, were unavailing. Hence, a literature review was conducted on various areas of nutritional management for VLBW infants including timing of feeding, feeding during indomethacin therapy for patent ductus arteriosus (PDA) closure, route of feeding (e.g. transpyloric or nasogastric tube feeds), type of feed, and feeding advancement. The literature review also focused on feeding related issues such as definition and management of feeding intolerance, and nursing management of enteral tube feedings. Application of current understanding of gastrointestinal ontogeny, as discussed in Chapter 2, has been integrated in the review.

MEDLINE, being the largest of the electronic services for the biomedical literature (Haynes et al., 1986) was the first computer search done. Kirpalani, Schmidt, McKibbon, Haynès, and Sinclair (1989) concluded that MEDLINE searches were not sensitive enough to be recommended as the only strategy for keeping abreast with the published literature. Consequently, similar searches were also conducted in Cumulative Index of Nursing in Allied Health Literature (CINAHL), Health, and the Cochrane Controlled
Trials register. Additionally, reference lists of all published journal articles on the question of interest were reviewed to identify other research articles.

Appropriate text word or medical subject headings (MeSH) used to conduct the electronic searches included: infant premature, nutrition, infant nutrition, enteral feeding, enteral nutrition, early enteral feeding, minimal enteral feeding, feeding, PDA, gastrointestinal motility/transit, gastric emptying, feeding tolerance, feeding intolerance, gastric residuals, NEC, continuous, intermittent, enteral nursing, infant-premature-metabolism, feeding methods, gastric residuals, tube feeding, weight gain, gastrointestinal hormones, motor activity, human milk, premature human milk, infant formula, and neurodevelopment. Terms used to limit the search included newborn infants, infant-newborn, infant low birth weight, human and English.

Methodologic terms were not incorporated into the searches as certain areas of nutritional management for premature infants are not well researched, for instance, feeding management during indomethacin therapy. Hence, rather then limiting the search with a methodologic term, a broad search was done. Additionally, Kirpalani et al. (1989) point out that randomized trials constitute only a small portion of all published results of studies. Since the intent was to retrieve a comprehensive list of all relevant research studies in the field, all phases of trials including randomized controlled trials, comparative studies, and descriptive studies were included in the search.

The electronic searches date back to 1966 for MEDLINE, 1982 for CINAHL, and 1975 for Health. The initial literature review was completed in March of 1998, prior to
the introduction of the guidelines which took place April 20th, 1998. The literature has been reviewed on an ongoing basis to ensure the continued validity of the guidelines. Reports published up to and including August 31, 1999 have been incorporated in the literature search in this chapter and continue to support the proposed guidelines. The relevant reports published after August 31, 1999 are cited in the discussion section of the thesis.

3.2 Literature Review

The various areas of nutritional management for infants <1500 grams examined in this section will expound upon the clinical relevance of gastrointestinal ontogeny pertinent to the specific area being discussed. Standard practice will be examined to determine whether it is consistent with the present understanding of gastrointestinal ontogeny and current research in the area. Recommendation(s) for the CPG and the relationship of the adopted strategy to the outcome(s) of this study will be presented in the summary.

3.2.1 Timing of feeding

Based on our current understanding of gastrointestinal ontogeny, one can postulate that withdrawal of enteral feeds after birth is unphysiologic (Lucas, 1993b). Enteral feeding should be initiated soon after birth for VLBW infants. Intraluminal stimuli, that is, enteral nutrition, stimulates secretion of many gastrointestinal hormones such as gastrin. According to Lucas, Bloom, and Aynsley-Green (1986), infants who are fasting lack hormonal responses. Surges in plasma concentrations of gut hormones postnatally may be important in maintaining drive to gut development (Lucas et al., 1986).
A pilot study conducted in a 33 bed, university-affiliated teaching hospital, NICU to delineate standard practice revealed great variability in timing of feeding (details of the study are presented in Appendix A). Feedings were commenced as early as Day 1 of life to as late as day 14. The data are summarized in Table 4. Although one can assert that initiation of feedings at day 14 lags behind our current understanding of the ontogeny of the gastrointestinal system, there is a need to determine the optimum timing of enteral feeding.

Enteral feeding has been classified as either early or minimal enteral nutrition (MEN). Early enteral feeding “is the attempt to achieve significant nutritional intake via the gut shortly after birth, to avoid or reduce parenteral nutrition” (Lucas, 1993b, p. 2). MEN refers to the “use [of] food not as a nutrient source but rather as a ‘medication’ to achieve biologic effects on the gut” (Lucas, 1993b, p. 3). MEN is also known as trophic feeds or induction feeds. A number of studies (Becerra et al., 1996; Berseth, 1992; Berseth & Nordyke, 1993; Dunn, Hulman, Weiner, & Kliegman, 1988; Meetze et al., 1992; Ostertag, LaGamma, Reisen, & Ferrentino, 1986; Slagle & Gross, 1988; Troche et al., 1995) have looked at MEN and its effect on measures of feeding intolerance such as days to full enteral feeding, total days that feedings were held and neonatal outcomes such as total hospital stay, serum direct bilirubin level and NEC. Table 5 summarizes the characteristics of these studies.

A systematic review done by Tyson and Kennedy (1998) found that among premature infants given MEN, there was an overall reduction in mean days to full enteral
Table 4. Pilot Study Data for Timing (in days) of Feeding

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>Sample Size</th>
<th>Mean ± Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 749 grams</td>
<td>6</td>
<td>6 ± 1.8</td>
<td>4 - 9</td>
</tr>
<tr>
<td>750 - 999 grams</td>
<td>16</td>
<td>4.7 ± 3.0</td>
<td>2 - 14</td>
</tr>
<tr>
<td>1000 - 1499 grams</td>
<td>36</td>
<td>3.3 ± 1.7</td>
<td>1 - 9</td>
</tr>
</tbody>
</table>
Table 5. Characteristics of Studies on Minimal Enteral Feeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Becerra et al., 1996</th>
<th>Berseth, 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized</td>
<td>Randomized</td>
</tr>
<tr>
<td>n</td>
<td>313; EES=161; Control=152</td>
<td>27; Early fed=14; Late fed=13</td>
</tr>
<tr>
<td>Subjects</td>
<td>AGA or SGA, VLBW infants. BW ≤ 1500 g. Infants divided into healthy or sick group based on predetermined criteria. Excluded infants with congenital malformations, metabolic disease and imminent risk of death.</td>
<td>Infants 28-32 weeks gestation requiring ventilation for RDS. Clinically stable (1-2 ventilator changes per day). ( F_{O_2} &lt; 0.40 ). No congenital anomalies.</td>
</tr>
<tr>
<td>Intervention</td>
<td>EES = 25 cc/kg per day of breast milk or formula enterally for healthy infants. EES started at 12-24 hours and continued for 48 hours. Sick infants, EES, started at 36-48 hours and continued for 6 to 8 days of life. After this period, for both groups, feed advanced at a rate of ≤ 20 cc/kg per day. Breast milk was fortified after 100 cc/kg per day was reached.</td>
<td>Early fed infants received Similac 20 16 kcal/kg per day at day 3-5 until 10-14 days. Late fed infants received 16 kcal/kg per day on day 10-14 days. In both groups feeds advanced by attending neonatologist. Both groups received 150 cc/kg per day.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Weight gain at 10-18 days better in EES. Feeding tolerance better in healthy EES group (&lt; nil per os hours in EES group). Hyperglycemia more severe in controls. No difference in days to recover BW, weight at 60 days, days to reach 2000 g, sepsis, prevalence of NEC, and overall mortality until discharge.</td>
<td>Study 1 (day 5) no significant difference in motor activity and fasting gastrointestinal peptide concentration between groups. Study 2 (day 10) early fed infants had significantly more mature motor patterns, significantly higher plasma concentration of gastrin and gastric inhibitory peptide than late fed infants. Neotensin and peptide YY values were similar in both groups. Study 3 (10-14 days after Study 2) no difference in gut development between groups. Early fed group able to tolerate full oral nutrition sooner, had fewer days of feeding intolerance and shorter hospital stay.</td>
</tr>
</tbody>
</table>

Abbreviations: appropriate for gestational age (AGA); birth weight (BW); early enteral stimulation (EES); fractional inspired oxygen \( (F_{O_2}) \); necrotizing enterocolitis (NEC); respiratory distress syndrome (RDS); small for gestational age (SGA); very low birth weight infants (VLBW)
### Table 5. Characteristics of Studies on Minimal Enteral Feeding ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Becerra et al., 1996</th>
<th>Berseth, 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Abstract only. Method of randomization not stated. Unsure if caregivers and data collectors were blinded. Largest trial.</td>
<td>Method of randomization not stated. Caregivers not blinded. State that feeding between Studies 2 and 3 uniformly managed; however, elsewhere state feeds advanced as per neonatologist. Technician analyzing manometric tracings blinded. Feeding intolerance not well defined. Small sample size.</td>
</tr>
<tr>
<td>Study</td>
<td>Berseth and Nordyke, 1993</td>
<td>Dunn et al., 1988</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized</td>
<td>Stratified in 1 of 4 weight categories: 750 g, 750-999 g, 1000-1249 g, 1250-1500 g. Within each category, random assignment to groups by “cards in paired envelopes”.</td>
</tr>
<tr>
<td>n</td>
<td>32; MEN=16; Control=16</td>
<td>39; NPO=20; enteral feeding=19</td>
</tr>
<tr>
<td>Subjects</td>
<td>26-33 weeks AGA infants with RDS, no congenital anomalies.</td>
<td>All infants &lt; 1500 g with respiratory distress who required mechanical ventilation and placement of UAC. Infants excluded if they had serious congenital anomalies and postnatal age &gt; 48 hours.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Small volume of feed (24 cc/kg per day) given to MEN group and equal volume of water given to control group. Daily caloric intake same for both groups (120 cal/kg = enteral and parenteral roules). Water fed infants given formula feeding after 10 days; volume advanced according to NICU routine.</td>
<td>NPO group received no enteral nutrition until 9 days of age. Enteral feeding group fed 15-20 cc/kg per day half strength Enfamil, initiated at 48 hours and continued until day 9. Both groups received same parenteral nutrition.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>After 10 days, change in motor response to feeding in MEN group; no change in control group. In control group, after 2 weeks of formula feeding, motor response to feeding restored and motor activity pattern similar to infant in MEN group. No significant difference in feeding intolerance and days feeds interrupted. Infants in MEN group established full feeds and nipple feeding sooner; regained BW sooner; and were discharged sooner.</td>
<td>Enteral feeding group reached full enteral feeding earlier, had fewer days under phototherapy and greater decline in serum bilirubin level over 2 weeks of life, had less cholestasis and had less osteopenia of prematurity (manifested by lower alkaline phosphate levels). No significant difference in days on TPN, number of days with feeding intolerance, days to regain BW, growth, weight difference between groups, total caloric intake, incidence of NEC.</td>
</tr>
</tbody>
</table>

Abbreviations: appropriate for gestational age (AGA); birth weight (BW); minimal enteral nutrition (MEN); necrotizing enterocolitis (NEC); neonatal intensive care unit (NICU); nothing by mouth (NPO); respiratory distress syndrome (RDS); total parenteral nutrition (TPN); umbilical arterial catheter (UAC)
Table 5. Characteristics of Studies on Minimal Enteral Feeding ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Berseth and Nordyke, 1993</th>
<th>Dunn et al., 1988</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Method of randomization unknown. Unclear if caregivers and data collectors were blinded. Definition of feeding intolerance somewhat subjective. Small sample size.</td>
<td>Account for infants who did not complete study. Study appears to be quasi-randomized. Unsure if data collector(s) were blinded. Subjective definition of feeding intolerance. Full strength formula introduced if feeds tolerated for 48 hours. Do not state if there were differences between groups in timing of full strength formula. Small sample size.</td>
</tr>
<tr>
<td>Study</td>
<td>Meetze et al., 1992</td>
<td>Ostertag et al., 1986</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized. Stratified into BW groups prior to random assignment.</td>
<td>Randomized</td>
</tr>
<tr>
<td>( n )</td>
<td>40; total parental nutrition=21; MEN=19</td>
<td>38; Early=18; Late=20</td>
</tr>
<tr>
<td>Subjects</td>
<td>BW 500-1250 g and gestational age 25-32 weeks. Infants with congenital or acquired disease of gastrointestinal tract and breast fed babies were excluded.</td>
<td>Infants &lt; 1500 g categorized as high risk for NEC by scoring system (score of ( \geq 6 )). One point given for each of the following: BW &lt; 1500 g, BW &lt; 1000 g, gestational age &lt; 32 weeks, 5 minute Apgar score &lt; 6, need for oxygen, need for ventilatory assistance, suspected IVH, presence of seizures, PDA and UAC.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Both groups received same total parental nutrition. MEN group received full strength formula 2 kcal/kg per day (2.5 cc/kg per day) on day 3 and increased to 18 kcal/kg per day on day 14 (bolus feedings given every 2 hours). On day 15, both groups received 20 kcal/kg per day (25 cc/kg per day) and increased 20 kcal/kg per day to a maximum of 120 kcal/kg per day by day 20, thereafter maintained same until day 30.</td>
<td>Early fed group on day 1 received continuous infusion of sterile water, progressing to 2.5% dextrose, half strength and finally full strength formula over 7 day period. Subsequent advances in volume made according to “infants’ condition”, attempted to increase 10 cc/kg per day until reached 150 cc/kg per day.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in enteral intake and caloric intake during first 30 days, weight gain, feeding complications, serum protein, albumin, pre-albumin, total bilirubin, direct bilirubin, calcium, phosphorus, or alkaline phosphatase levels. MEN group had improved feeding tolerance after day 20, faster rise in serum gastrin.</td>
<td>No significant difference in incidence of NEC. No significant relationship between onset of feeding and incidence of NEC. Early fed group had significantly higher energy and protein intake during the 2 weeks of life.</td>
</tr>
</tbody>
</table>

Abbreviations: birth weight (BW); intraventricular hemorrhage (IVH); minimal enteral nutrition (MEN); necrotizing enterocolitis (NEC); patent ductus arteriosus (PDA); umbilical arterial catheter (UAC)
Table 5. Characteristics of Studies on Minimal Enteral Feeding ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Meetze et al., 1992</th>
<th>Ostertag et al., 1986</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Method of randomization not stated. No intention-to-treat analysis, excluded</td>
<td>Scale used to categorize infants as high or low risk validated previously. Random</td>
</tr>
<tr>
<td></td>
<td>infants who developed NEC or were transferred prior to 20 days. Unsure if total</td>
<td>number table used to assign infants. Feeds increased subjectively. Radiologist</td>
</tr>
<tr>
<td></td>
<td>nutrition refers to total parental nutrition and enteral feeds. Attempted to define</td>
<td>interpreting abdominal x-rays blinded. Number of radiologist(s) not stated. Criteria</td>
</tr>
<tr>
<td></td>
<td>feeding intolerance objectively. Did not state what proportion of infants were</td>
<td>used for diagnosing NEC not stated. No definition of feeding intolerance. All subjects</td>
</tr>
<tr>
<td></td>
<td>mechanically ventilated. Small sample size.</td>
<td>accounted for including those excluded.</td>
</tr>
</tbody>
</table>

Abbreviations: necrotizing enterocolitis (NEC)
Table 5. Characteristics of Studies on Minimal Enteral Feeding ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Slagle and Gross, 1988</th>
<th>Troche et al., 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized</td>
<td>Randomized</td>
</tr>
<tr>
<td>n</td>
<td>46; Early=22; Late=24</td>
<td>29; NPO=13; Early=16</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants at risk for NEC identified by following criteria: BW 500-1500 g, gestational age ≤ 32 weeks, requirement of mechanical ventilation for ≥ 3 days, requirement of supplemental oxygen for ≥ 7 days, at least 2 of 4 additional risk factors including 5 minute Apgar ≤ 5, UAC, hypotension treated with volume expanders, and PDA requiring medical and surgical treatment in first week of life.</td>
<td>Infants 25-30 weeks gestational age with RDS, UAC insitu, and anticipated need for mechanical ventilation for at least 3 days. Infants excluded if they had persistent hypoxemia (P_{O_2}, 45 mmHg) or hypercarbia (P_{CO_2} &gt; 60 mmHg, acid-base status, 7.25) despite aggressive ventilation, known gastrointestinal anomalies, severe asphyxia (5 minute Apgar ≤ 3), persistent hypotension, or CHD with decreased left sided outflow.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Both groups received same total parental nutrition. Caloric intake from total parental nutrition and enteral feeds same in both groups. Day 7 early fed group received 12 cc/kg per day milk feeding every 2 hours. Day 18 feeding advancement in both groups uniform, began at 15 cc/kg per day and increased 15 cc/kg per day until reached 180 cc/kg per day.</td>
<td>Early group fed mother's milk or Similac formula prior to 24 hours of age. Feeding advanced from 0.5 cc per hour to 0.75 cc per hour (&lt; 800 g BW) or 1.0 cc per hour (800-1200 g BW) at 24 hours. Rate was maintained until UAC removed and standard feeding initiated per protocol. Continuous infusion feeds for &lt; 800 g BW and bolus feeds given every 3 hours for 800-1200 g BW infants.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in days to full enteral feeds, peak total serum bilirubin concentration, days to regain BW. Early fed infants able to tolerate significantly greater enteral intakes. Early fed infants had significant decrease in number of days: gastric residuum was &gt; 10% of feeding, feedings were held for feeding intolerance, and on total parental nutrition.</td>
<td>No significant difference in: mean number of episodes of feeding intolerance per infant during first 30 days, changes in somatomedin C levels with postnatal age or growth, or serum diamine oxidase levels. Early fed infants reached 120 cc/kg per day or enteral feeding sooner than NPO group. By day 30, early fed group had gained significantly more weight over BW than NPO group, early fed infants had a greater caloric intake than did NPO group infants on days 1-30.</td>
</tr>
</tbody>
</table>

Abbreviations: arterial carbondioxide pressure (P_{CO_2}); arterial oxygen pressure (P_{O_2}); birth weight (BW); congenital heart disease (CHD); necrotizing enterocolitis (NEC); nothing by mouth (NPO); patent ductus arteriosus (PDA); respiratory distress syndrome (RDS); umbilical arterial catheter (UAC)
Table 5. Characteristics of Studies on Minimal Enteral Feeding ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Slagle and Gross, 1988</th>
<th>Troche et al., 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Infants assigned randomly by selection of cards in sealed envelopes. Attempted to define feeding intolerance objectively. Unsure if radiologist interpreting x-rays for NEC was blinded.</td>
<td>Used random number table to assign infants. Unsure if randomization was blinded. Subjective definition of feeding intolerance. Male-to-female ratio differed significantly, however, unsure of its implications. Small sample size.</td>
</tr>
</tbody>
</table>

Abbreviations: necrotizing enterocolitis (NEC)
feeding, total days that feedings were held, and total hospital stay. The weighted mean
differences were 2.7 days, 3.1 days, and 15.6 days, respectively. The authors also report
inconsistency in the treatment effect for variables such as days to full enteral feeding and
days to regain birth weight. These inconsistencies resulted in statistical heterogeneity
which was thought to be due to differences in findings between Becerra et al. (1996) and
those of other trials. The Becerra et al. trial was the largest study (n = 190), however, the
infants in this study appear to be less ill compared to infants in the other trials. All other
trials had small sample sizes with <45 subjects (Tyson & Kennedy, 1998).

Characteristics of studies differed in other ways. The inclusion criteria varied across
studies and included gestational age (Berseth, 1992; Troche et al., 1995), birth weight
(Becerra et al., 1996; Dunn et al, 1988), both gestational and birth weight (Berseth &
Nordyke, 1993; Meetze et al., 1992; Slagle & Gross, 1988), or a scoring system (Ostertag
et al., 1986). The operational definition of MEN also varied across studies. Infants in the
MEN group received as little as 12 cc/kg per day (e.g. Slagle & Gross, 1988) to as much
as 24 cc/kg per day of feed (e.g. Berseth, 1992) which consisted of either dilute (e.g.
Dunn et al., 1988) or full strength formula (e.g. Berseth, 1992; Meetze et al., 1992) or
breast milk (e.g. Berseth, 1992). Ostertag et al. (1986) started with sterile water and
progressed to 2.5% dextrose, half-strength formula, and then full strength formula. MEN
started as early as the first day of life or as late as the eighth day of life. The MEN
protocol continued for 5 to 10 days. The control group received no enteral nutrient intake
of milk; some did, however, receive water only. These varied interventions could explain
the inconsistencies noted in treatment effect for variables related to feeding tolerance, such as days to full enteral feeding, as both starvation (Lucas et al., 1983, 1986; Sharma et al., 1995) and dietary factors (Ewer, Durbin, Morgan, & Booth, 1994; Husband & Husband, 1969; Siegel, Krantz, & Lebenthal, 1985; Siegel, Lebenthal, & Krantz, 1984) have an impact on the gastrointestinal system.

Tyson and Kennedy (1998) mention additional caveats to the interpretation of outcome measures of feeding intolerance, weight gain, and discharge from hospital. These caveats include the lack of an objective definition of feeding intolerance, care-giver bias in operationally defining feeding intolerance, and lack of inclusion of all patients in the outcome assessment. Infants who developed complications were excluded from the analysis in some studies (Dunn et al., 1988; Slagle & Gross, 1988) which may bias the above mentioned outcomes.

With respect to the outcome of NEC, MEN has no significant effect as the relative risk was 1.10, with a 95% confidence interval of 0.63 to 1.90. However, limitations of the available studies requires a cautious interpretation of findings as one could erroneously conclude that no difference existed when in fact there was a difference; type II error. As well, MEN may have a significant effect on the outcome of NEC but the studies were unable to detect the difference because of the small sample size and low incidence of NEC, that is, the studies lacked sufficient power to detect the difference. Hence, it makes it difficult to rule out the possibility that MEN increases the likelihood of NEC (Tyson & Kennedy, 1998). Additional reasons for prudently interpreting the analyses of the
outcome of NEC include, variability in incidence of NEC among centers, diagnostic surveillance bias because of care giver bias of monitoring a particular weight group of infants more closely, evaluator bias, that is, x-ray interpretation bias, if the clinician is not blinded to infant feeding, and inter-observer variation of x-ray findings even if observer is blinded (Tyson & Kennedy, 1998). The identification of NEC on x-ray was blinded in Slagle and Gross’s (1988) study. It is unclear if similar measures of blinding were utilized in other studies. Another limitation of the MEN feeding studies is that they fail to report confounding variables such as use of indomethacin for PDA closure, which may be associated with an increased incidence of NEC (Hay, 1996). It is important that such confounding variables are randomly and equally present amongst infants in the MEN group and delayed feeding group (Hay, 1996).

The MEN feeding studies and systematic review cannot affirm the beneficial effects of MEN because of the uncertainty about the effect of MEN on NEC, lack of consistent results across trials, and methodological limitations of trials (Tyson & Kennedy, 1998). If MEN is implemented in practice, it is important to monitor its efficacy and safety.

In summary, current knowledge of gastrointestinal ontogeny supports initiation of feedings soon after birth of VLBW infants. The biological or physiologic basis of the beneficial effects of MEN do appear plausible and the meta-analysis does suggest certain benefit. MEN will be incorporated in the CPG developed for the nutritional management of premature infants < 1500 grams as standard practice does not reflect current knowledge of gastrointestinal development and research in the area of timing of feeding.
Given the variability in the literature with regards to the initiation and duration of MEN, consensus decision-making will be employed to determine the protocol for the CPG.

To assess compliance with CPG, timing of first feed, in days, will be measured. To verify the efficacy of the strategy of MEN adopted in the CPG, days to regain birth weight, as well as variables related to feeding intolerance including number of feeding interruptions, days on TPN, and days to full feeds will be measured. Additionally, adverse effects, such as NEC will be monitored to assess the safety of this strategy.

3.2.2 Feeding during indomethacin therapy for PDA closure

Current practice is to withhold enteral feeding during indomethacin therapy. At present, there are no data to support the practice of withholding enteral feeding when indomethacin therapy is initiated. It is, however, best to withhold enteral feeding when there is concern about blood flow to the gastrointestinal tract (Hay, 1996) because ischemic mucosal injury is a common factor in the etiology of NEC (Brown & Sweet, 1982; Bauer et al., 1984). Ischemic mucosal injury can lead to increased permeability to antigens, bacteria, viruses, and toxins, in an already compromised immature intestinal host defense system, resulting in a inflammatory cascade response recognized as NEC (Israel, 1994). Premature infants with symptomatic PDA have reduced, absent, or retrograde mesenteric diastolic blood flow velocities (Coombs, Morgan, Durbin, Booth, & McNeish, 1990; Shimada, Kasai, Konishi, & Fujiwara, 1994) and these reductions are further amplified with indomethacin therapy (Coombs et al., 1990; Van Bel, Van Zoeren, Schipper, Guit, & Baan, 1990; Yanowitz et al., 1998). Therefore, premature infants
receiving indomethacin therapy for PDA are likely to have decreased blood flow to the gastrointestinal system, hence, at increased risk of NEC. A systematic review conducted by Fowlie (1997) found a trend towards increased incidence of NEC in infants, birth weight < 1751 grams, who received prophylactic intravenous indomethacin.

One study examined the effect of enteral feed, 1 to 3 cc of premature infant formula per feeding, given 1 hour after the third dose of prophylactic indomethacin (0.1 mg/kg administered at 6, 30, and 54 hours of life) on mesenteric diastolic blood flow velocities. The mesenteric diastolic blood flow velocities, measured 30 minutes after the feed, increased postprandially even though the volume of formula administered was minimal and there was reduced mesenteric diastolic blood flow velocity post prophylactic indomethacin therapy (Yanowitz et al., 1998). One could postulate that MEN may be beneficial during indomethacin therapy as it would counteract the reduced mesenteric diastolic blood flow associated with this therapy. Hence, MEN may serve a protective role in that it would decrease the risk of ischemia associated with reduced mesenteric diastolic blood flow. According to Yanowitz et al. (1998), "further investigations are needed to better characterize the normal mesenteric blood flow velocity response to feeding in [VLBW] infants and the effects of indomethacin on this response" (p. 33).

*In summary, although some research suggests a benefit of MEN on mesenteric diastolic blood flow, until further research supports a change in practice, a conservative approach of not feeding VLBW during indomethacin therapy will be adopted in the CFG.*

*This conservative approach stems from the impending concern of NEC secondary to*
ischemic mucosal injury resulting from indomethacin therapy. NEC will be monitored in this study to assess the safety of this strategy. Additionally, when there is concern about ischemic mucosal injury secondary to vascular compromise, as may be the case in infants who have an Apgar score of ≤ 3 at 5 minutes of age and infants who are intrauterine growth restricted (IUGR), the use of CPG will be deferred and these babies will be excluded from the study.

3.2.3 Route of feeding

Based on our current understanding of gastrointestinal ontogeny, coordinated sucking and swallowing reflex is not fully developed until approximately 34 weeks gestation (Dumont & Rudolph, 1994). Even at 32 weeks gestation, esophageal motility is not coordinated and the motility activity is similar to that seen in older children with gastroesophageal reflux and dysmotility (Gryboski, 1965). Accordingly, tube feeding is necessary for premature infants < 1500 grams. Although standard practice embraces the practice of tube feeding VLBW, the method of feeding varies. While the intermittent bolus gavage feeding method is used more commonly in practice, the continuous nasogastric tube feeding method is prescribed, by some clinicians, for infants who are experiencing feeding difficulties, such as persistent large volume residuals despite manipulation of amount of feeding and frequency of feeding. When feedings are given by the method of intermittent bolus gavage, the nasogastric tube remains indwelling, that is, in place until it needs to replaced as per unit policy, which is every 72 hours, or is accidentally removed.
Research findings indicate that the method of feeding could affect the ability of the premature infant's gastrointestinal system to handle nutrients, as well as the metabolic response to feeding (Lucas, 1993a). Intraduodenal and nasojejunal feeding, forms of transpyloric feeding method, are not used routinely for feeding premature infants. From a practical clinical perspective, positioning of the transpyloric feeding tube requires a trained individual, the procedure is technically difficult and does not always result in transpyloric passage of the feeding tube, and it may expose the infant to additional x-rays to verify tube position (Drew, Johnston, Finocchiaro, Taylor, & Goldberg, 1979; Laing, Lang, Callaghan, & Hume, 1986; Pereira & Lemons, 1981; Steer et al., 1992). Additionally, studies have not shown consistent improvements in outcomes of enteral energy intake and growth, including percent weight loss, days to regain birth weight, and postnatal weight gain (Steer et al., 1992). In two studies, energy intake was found to be lower with transpyloric feeding (Drew et al., 1979; Pereira & Lemons, 1981). The transpyloric feeding method has been shown to cause a statistically significant increase in death rate by meta-analysis with an absolute increase of 14.6% (95% confidence interval 5.4, 23.8%) (Steer et al., 1992). Steer et al. concluded that transpyloric feeding should not be used routinely in practice for feeding low birth weight infants.

The conventional tube feeding method is the intermittent bolus gavage feeding where a prescribed volume of milk is given over a short period of time (Aynsley-Green, Adrian, & Bloom, 1982), usually over 10 to 20 minutes by gravity. The first reported use of the continuous nasogastric tube feeding method for premature infants was in 1972 by Valman,
Heath, and Brown (Toce, Keenan, & Homan, 1987). However, Valman et al. (1972) reports that this method of providing a continuous hourly infusion of milk was first suggested in 1960 by D. Hilson. Some clinicians prefer the continuous nasogastric feeding method for feeding premature infants < 1200 to 1300 grams birth weight (Toce et al., 1987), although the intermittent bolus gavage feeding is the method most commonly used in practice (Churella, Bachhuber, & MacLean, 1985).

Continuous nasogastric compared to intermittent bolus gavage feedings may be more energy efficient (Grant & Denne, 1991), reduce feeding intolerance, improve nutrient absorption, and improve growth (Toce et al., 1987). However, continuous infusion of milk into the gut can alter the cyclical pattern of release of gut hormones that in turn may affect metabolic homeostasis, and possibly growth (Aynsley-Green et al., 1982). When human milk is given by continuous nasogastric feeding method, fat not only adheres to the delivery vessel, it also separates and rises up the feeding tube towards the syringe, consequently, may never be received by the infant. If the syringe infusing human milk is placed above the infant, 33% of human milk energy can be lost over a 40 hour period (Lucas, 1993a). Furthermore, a properly functioning LES is an important barrier against the reflux of stomach contents into the esophagus and aspiration. The problem of reflux and aspiration may be magnified in premature infants receiving continuous nasogastric feedings. Not only do these infants have reduced LES pressure (Newell et al., 1988), but the nasogastric tube remains in situ preventing complete closure of the sphincter.

Reflux is usually clinically "silent" as no discrete symptoms occur during the episode
(Hyman, 1994, p. S103). Controversy exists regarding the association of apnea with reflux both in relationship to the timing of apnea to reflux and the mechanism involved (Herbst, 1981; Newell, 1996). The mechanism is likely a vagally mediated reflex (Newell, 1996). A randomized controlled trial examining the effect of type of tube placement, intermittent versus indwelling, on weight gain, apnea, and bradycardia revealed no statistical or clinical differences between infants in the two groups. Infants 24 to 34 weeks gestational age (n = 93), appropriate for gestation age, were assigned randomly to either intermittent or indwelling tube placement when they were medically stable, on full enteral feedings, and not fluid restricted, and were followed for 6 days. The CPG study setting was one of the study settings in this randomized controlled trial; others were a secondary level NICU and a tertiary level NICU in a referral center. The authors concluded that “type of tube placement may be based on economics” (p. 321) given the findings of their study (Symington, Ballantyne, Pinelli, & Stevens, 1995). Consequently, the indwelling method was chosen as standard practice as it is most cost-effective. Interpretation of this study is limited by the fact that it failed to consider potential interactions with other areas of nutritional management, for instance, gut priming or MEN, and early versus late nutritional feeding.

Intermittent bolus gavage feedings are thought to be more physiologic because they promote the cyclical surges of gut hormones normally seen in healthy term infants (Aysnley-Green et al., 1982; Aysnley-Green, Lucas, Lawson, & Bloom, 1990). Gastrointestinal hormones such as gastrin, gastric inhibitory peptide, and enteroglucagon
are trophic and require the presence of intraluminal nutrients to stimulate secretion. Surges in plasma concentrations of gut hormones postnatally may be important for gut development (Aynsley-Green, 1989; Lucas et al., 1986). On the other hand, functional limitations of the premature infant’s gastrointestinal system, such as delayed gastric emptying or intestinal transit, could hinder the premature infant’s ability to handle bolus milk feeds, resulting in feeding intolerance. Additionally, this feeding regimen alternates between periods of feeding and fasting which could challenge the premature infant’s ability to maintain metabolic homeostasis, and limit growth (Aynsley-Green et al., 1982).

Continuous nasogastric tube feeding and intermittent bolus gavage feeding are compared in seven studies (Toce et al., 1987; Krishnan & Satish, 1981; Akintorin et al., 1997; Macdonald et al., 1992; Silvestre, Morbach, Brans, & Shankaran, 1996; Schanler, Shulman, & Lau, 1996; Urrutia & Poole, 1983). However, no systematic research overview has been conducted that synthesizes this literature. Table 6 summarizes the characteristics of these studies which differ in many ways, including randomization process, calculation of sample size, outcomes, and ways in which confounding variables were either measured or controlled (e.g., study design). Hereinafter is a critical appraisal of these studies.

Random allocation ensures that no systematic bias is introduced in the groups, thereby, ensuring equal distribution among groups of variables which may potentially affect the outcome of interest (Polit & Hungler, 1983). Toce et al. (1987) used alternate-assignment to facilitate the randomization process. To obtain a greater degree of
Table 6. Characteristics of Studies on Continuous Versus Intermittent Bolus Gavage Feeding Method

<table>
<thead>
<tr>
<th>Study</th>
<th>Akintorin et al., 1997</th>
<th>Krishnan and Satish, 1981</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Stratified into 2 BW groups: 700-1000 g and 1001-1250 g. Then randomly assigned to 2 feeding methods.</td>
<td>Quasi-Experimental</td>
</tr>
<tr>
<td>n</td>
<td>80; C=39; I=41</td>
<td>29; C=12; I=17</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants between 700-1250 g BW, hemodynamically stable and ready to start enteral feeds. Excluded if Apgar score &lt; 3 at 5 minutes, to receive breast milk, documented sepsis, NEC or unable to start feedings before day 10 of life.</td>
<td>Infants &lt; 1250 g.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Feeds did not begin until UAC removed. Continuous feeding by infusion pump. Intermittent feeding given every 3 hours for 15-30 minutes by gravity via indwelling feeding tube. Feeding protocol for each 50-100 g weight category.</td>
<td>Continuous versus intermittent gavage feeding method, not described.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No statistically significant difference in days to reach full feeding, days to regain BW, days to reach discharge weight and number of episodes of feeding intolerance.</td>
<td>No significant difference in tolerance to feeds or days to regain BW. Infants in C group achieved 90 cal/kg per day of oral feeds and steady weight gain sooner than infants in I group.</td>
</tr>
<tr>
<td>Comments</td>
<td>No significant difference in day of onset of feeding. Sequentially numbered opaque sealed envelopes, and table of random number used to assign infants. Feeding intolerance very objectively defined. Controlled for key confounders (e.g. feeding practice) though, not NNS. Calculated sample size.</td>
<td>Abstract only. Unsure if infants randomized. Small sample size. Question if this is a retrospective study. No definition of steady weight gain or feeding intolerance given.</td>
</tr>
</tbody>
</table>

Abbreviations: birth weight (BW); continuous nasogastric tube feeding method (C); intermittent bolus gavage feeding method (I); necrotizing enterocolitis (NEC); non-nutritive sucking (NNS); umbilical arterial catheter (UAC)
<table>
<thead>
<tr>
<th>Study</th>
<th>Macdonald et al., 1992</th>
<th>Schanler et al., 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized</td>
<td>Randomized Stratified by gestational age and intent to breast feed.</td>
</tr>
<tr>
<td>n</td>
<td>43; C=13; I=15; T=15</td>
<td>158; C=77; I=81</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants &lt; 1400 g. Excluded if receiving breast milk, had congenital anomalies, developed hydrocephalus or if they had intrauterine viral infection.</td>
<td>Premature infants BW 1.0 ± 0.2 kg (mean ± standard deviation). Gestation age 28 ± 1 week.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Day 2 feeds started with 1 cc per hour of SMA preterm formula, increased 0.5 to 1 cc per hour until tolerating 150 cc/kg per day. Once 1600 g, received bolus feeding Received TPN.</td>
<td>Continuous versus bolus tube feeding; not described.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference between groups in time to achieve full enteral feeding and growth parameters (e.g. weight, length). More complications T group.</td>
<td>Infants in I group achieved full feeds sooner, required less therapy for reflux, and had less feeding intolerance. No significant difference in absorption and nitrogen retention, fat, calcium, phosphorus, zinc, or copper in both groups. Lactase activity, intestinal permeability and growth not affected by feeding method.</td>
</tr>
<tr>
<td>Comments</td>
<td>Sealed envelope for assignment. Not sure if randomly assigned. Protocol for intermittent feeds not described. No definition of feeding intolerance. Do not describe how feeding intolerance was managed. Criteria for NEC not described. Unsure if data collectors were blinded.</td>
<td>Abstract only. Do not state how infants were randomized. Feeding intolerance not defined. Do not describe how feeding was approached in both groups; including management of feeding intolerance. Unsure if data collectors were blinded.</td>
</tr>
</tbody>
</table>

Abbreviations: birth weight (BW); continuous nasogastric tube feeding method (C); intermittent bolus gavage feeding method (I); necrotizing enterocolitis (NEC); total parenteral nutrition (TPN); transpyloric feeding method (T)  cont’d
Table 6. Characteristics of Studies on Continuous Versus Intermittent Bolus Gavage Feeding Method ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Silvestre et al., 1996</th>
<th>Toce et al., 1987</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Stratified by BW. Then randomly assigned.</td>
<td>Quasi-Experimental Alternate assignment of infants within 16 groups stratified according to BW category (&lt; 1250 g, 1250-1500 g) sex, IUGR and prior need for ventilation.</td>
</tr>
<tr>
<td>n</td>
<td>82; C=42; I=40</td>
<td>53; C=30; I=23</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants AGA with BW 750-1500 g, born between 27-34 weeks gestation, had no major congenital malformations and stable to start feeds on day 2 or 3 of life.</td>
<td>Infants &lt; 1500 g, free from major congenital anomalies, no longer ventilated, and ready for enteral nutrition.</td>
</tr>
<tr>
<td>Intervention</td>
<td>C group received 2 hours of feeding with water followed by half strength Similac (40 Kcal per day) formula 0.75 cc/kg advanced by 1 cc every 12 hours. Advanced to 3/4 strength on day 6 and full strength on day 9. I group received two consecutive feedings with water then same as above. Feeds given every 3 hours over 15-30 minutes, same as above.</td>
<td>Continuous feeds delivered by infusion pump. Intermittent feeds every 3 hours, allowed to drip by gravity. Test feeding with sterile water followed by hypotonic cow’s milk based formula for 3 days then given isotonic formula (SMA 20). Feeds started at 24 cc/kg per day, increased to 180 cc/kg per day by day 7.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in days to regain BW, days to full enteral feedings, days to discharge, and anthropometric measurements between groups.</td>
<td>No significant difference in occipitofrontal circumference, triceps skin-fold thickness, bilirubin values, total protein values, or feeding complications. Continuous feeding associated with significantly increased weight gain in infants 1000-1249 g BW.</td>
</tr>
</tbody>
</table>

Abbreviations: appropriate for gestational age (AGA); birth weight (BW); continuous nasogastric tube feeding method (C); intermittent bolus gavage feeding method (I); intrauterine growth restriction (IUGR)
### Table 6. Characteristics of Studies on Continuous Versus Intermittent Bolus Gavage Feeding Method ... cont'd

<table>
<thead>
<tr>
<th>Study</th>
<th>Urrutia and Poole, 1983</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Quasi-Experimental</td>
</tr>
<tr>
<td>n</td>
<td>43; C=17; I=26</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants ≤ 1500 g, ≤ 34 weeks gestation. Excluded infants who died within first 30 days of life, required ventilatory support for ≥ 2 ½ months, or had congenital anomalies.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Continuous versus intermittent gavage feedings, not described.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in days to regain BW, days to regain 1800 g or 2000 g.</td>
</tr>
<tr>
<td>Comments</td>
<td>Abstract only. Assignment to group based on neonatologist’s preference. Unsure if outcome assessors blind to intervention. Unequal distribution of patients in two groups. Definition of feeding intolerance and management of problem not described.</td>
</tr>
</tbody>
</table>

Abbreviations: birth weight (BW); continuous nasogastric tube feeding method (C); intermittent bolus gavage feeding method (I) cont’d
representation such that the sample is divided into homogeneous subsets (Polit & Hungler, 1983), studies stratified infants by birth weight (Akintorin et al., 1997; Silvestre et al., 1996), or by gestational age and intent to breast feed (Schanler et al., 1996) prior to randomization. In two studies (Krishnan & Satish, 1981; Urrutia & Poole, 1983), the effect of the feeding method on the outcomes of interest is difficult to establish because of the study design. One study was retrospective (Krishnan & Satish, 1981) and the other study, although prospective (Urrutia & Poole, 1983), patients were allocated to the continuous or intermittent group based on neonatologist’s preference rather then being randomly assigned.

A predetermined sample size is critical in order to achieve both clinical and statistical significance in a study (Raudonis & Talbot, 1995). It appears that convenience sampling was employed by some studies (Toce et al., 1987; Krishnan & Satish, 1981; Urrutia & Poole, 1983; Schanler et al., 1996). Only three studies reported the use of a power calculation to determine sample size (Macdonald et al., 1992; Akintorin et al., 1997; Silvestre et al., 1996).

Some studies detected no difference in weight gain (Toce et al., 1987; Macdonald et al., 1992; Silvestre et al., 1996; Schanler et al., 1996), days to regain birth weight (Akintorin et al., 1997; Silvestre et al., 1996; Urrutia & Poole, 1983), length (Toce et al., 1987; Macdonald et al., 1992; Silvestre et al., 1996), head circumference (Toce et al., 1987; Macdonald et al., 1992; Silvestre et al., 1996), or skin fold thickness (Toce et al., 1987; Silvestre et al., 1996) between the two methods of feeding. Toce et al. (1987) did,
however, show improvement in weight gain in the 1000 to 1249 gram subgroup of infants. Krishnan and Satish (1981) found that infants fed by continuous nasogastric tube feedings reached 90 Kcal/kg per day (376 Kjoul/kg per day) almost twice as quickly as those infants fed by intermittent bolus gavage feeding method (16 ± 6 vs 26 ± 17 days, respectively, p < 0.05). As well, infants in the continuous group had better weight gain then infants in the intermittent group (24 ± 10 vs 32 ± 14 days, p = 0.05).

Some studies either controlled or measured variables which might have influenced the outcomes of interest. Toce et al. (1987) controlled the nutrient intake in both the experimental and control group to better understand the influence of each feeding method on weight gain. Rather then controlling nutrient intake, other studies measured energy intake and found no difference in energy intake between infants in the bolus nasogastric group versus continuous nasogastric group (Macdonald et al., 1992; Silvestre et al., 1996). These studies found no difference in the outcomes of interest between the two groups. Krishnan and Satish (1981) did not control energy intake in their study, hence, their findings although positive, are difficult to interpret.

Improved weight gain has been reported in premature infants who were encouraged to suck on a pacifier during gavage feeding (Bernbaum, Pereira, Watkins, & Peckham, 1983; Measel & Anderson, 1979; Field et al., 1982). Akintorin et al. (1997) is the only study which attempted to control this variable. In their study, infants in both feeding method groups were provided opportunities for NNS, however, they did not measure these opportunities. It is uncertain if equal opportunities were provided to infants in both
groups, thereby limiting the findings of this study which showed no difference between groups in the outcomes studied.

Some studies report no statistically significant effect of intermittent bolus gavage feedings versus continuous nasogastric tube feedings on days to full feeds (Akintorin et al., 1997; Macdonald et al., 1992; Silvestre et al., 1996), and number of episodes of feeding intolerance (Akintorin et al., 1997). In contrast, Schanler et al. (1996) found that the intermittent bolus method of feeding was better than the continuous method of feeding; the former was associated with more rapid attainment of full tube feeding and better feeding tolerance. Those infants receiving bolus feeds required anti-reflux therapy less often than those receiving continuous feeds (Schanler et al., 1996).

Enteral nutrition is important in maintaining mucosal morphology, and therefore, the functional characteristics of the gastrointestinal tract (Lucas et al., 1983; Sharma et al., 1995). Feeding promotes maturity of motor activity (Dumont & Rudolph, 1994), therefore, it is important to consider timing of feeds when assessing effects of the two feeding methods on days to full feeds, episodes of feeding intolerance, weight gain, and days to regain birth weight. Akintorin et al. (1997) developed feeding protocols for each 50 to 100 grams weight category and timing of feeds was similar in the 2 groups (intermittent 5.6 ± 2.2 days; continuous 5.7 ± 2.1 days). Urrutia and Poole (1983) also measured timing of feeds and found that the onset of feedings was similar in the 2 groups (10.6 ± 9.6 days intermittent; 11.1 ± 4.5 days continuous, p value not significant).

It is imperative that feeding intolerance be defined and a systematic approach
developed in the management of feeding intolerance. Studies defined feeding intolerance for each group and developed arbitrary guidelines based on consensus among the study staff and the attending neonatologists (Akintorin et al., 1997), or by approval of a review board and review committee of the institution (Toce et al., 1987). In some studies, the definition of feeding intolerance included amount of gastric residual, and clinical findings, such as abdominal girth and dilated loops of bowel, and x-ray findings (Akintorin et al., 1997; Toce et al, 1987). In other studies (Schanler et al., 1996), feeding intolerance was defined solely on gastric residuals. The former definition of feeding intolerance is comprehensive, and captures the fullness and complexity involved in decision making around withholding or continuing feeding. As well, it limits the subjectivity or bias introduced by the clinician. The latter definition although simple, allows considerable input from the clinician with regard to decision making around withholding or continuing feeds, thereby, introducing bias.

The health state of the infant can also affect some of the outcomes of interest, for example, days to discharge. Number of days on a ventilator was measured and no difference was found between groups (intermittent 9.4 ± 9.8 days; continuous 8.9 ± 10.9 days) (Akintorin et al., 1997). Weight was used as a measure of readiness for discharge by one study (Akintorin et al., 1997). In this study, the discharge weight was predetermined by the researchers, thereby eliminating bias. In one study it is unclear how the decision for discharge was made (Silvestre et al., 1996). No significant difference was found in length of hospital stay between infants in the two feeding methods (Akintorin et
al., 1997; Silvestre et al., 1996).

The current scientific literature in the area of feeding methods for premature infants < 1500 grams yields conflicting results. The studies reviewed are difficult to interpret as the research methodology was not sound, and studies had a small sample size and weak study design (e.g., retrospective study). Additionally, both known and unknown variables that may significantly affect the outcomes of interest were not consistently controlled, resulting from absence of randomization, stratification, and protocols for management of feeding intolerance. Although universal recommendations cannot be made with regard to the best method of tube feeding, the literature does indicate that the choice of feeding method can be based on clinical judgement.

In summary, the literature comparing intermittent bolus gavage feeding with continuous nasogastric tube feeding is of limited quality with evidence from some studies favoring the intermittent gavage feeding method and others favoring the continuous nasogastric tube feeding method. Since the current state of knowledge does not contradict standard practice, which is use of intermittent bolus gavage feeding method or continuous nasogastric tube feeding method based on clinical judgement, the CPG will not stipulate the tube feeding method for providing enteral nutrition. Additionally, tube feeding method will not be an outcome measure of this study. CPG will continue to subscribe to the indwelling type of tube placement method, which has been established as standard practice in the unit, as there is lack of evidence to support a change in practice. Type of tube placement method will not be an outcome measure of this study.
3.2.4 Type of feed

According to our current understanding of gastrointestinal ontogeny, at 25 weeks gestation the premature infant is capable of generating amplitudes of contractions capable of moving nutrients forward in the gastrointestinal tract (Dumont & Rudolph, 1994). The antrum, pylorus, and duodenum contract in a coordinated fashion to empty the liquid in the stomach. Alteration in the coordination of motor activity in these areas can result in delayed gastric emptying (Berseth, 1996; Houghton et al., 1988). Delayed gastric emptying and intestinal transit are important when considering enteral nutrition (Berseth, 1996). Delayed gastric emptying in premature infants frequently presents as failure to tolerate feeds, that is, feeding intolerance (Kelly & Newell, 1994). Feeding intolerance results in abdominal distention, vomiting, and feeding residuals (Gross & Slagle, 1993; Newell, Chapman, & Booth, 1993). Gastric emptying is better with breast milk (Ewer et al., 1994), glucose polymers, and medium chain triglycerides (Siegel et al., 1985), whereas emptying is delayed with increasing energy density (Siegel et al., 1984), higher fat, long chain triglycerides (Siegel et al., 1985), and greater dextrose (Husband & Husband, 1969). Since dietary factors are known to affect gastric emptying, it is imperative to scrutinize the VLBW infant’s response to various types of feed in order to endorse a specific type of feed for the CPG. Standard practice in the unit is to use expressed breast milk, however, if breast milk is unavailable, either because the parents have decided not to breast feed or supply is limited, then premature infant formula is used.

Studies using a marker dilution technique (Cavell, 1979, 1982) and ultrasonography
(Ewer et al., 1994) have shown that breast milk empties faster than formula. In fact, the rate of gastric emptying of breast milk is reported to be as high as twice that of formula (Ewer et al., 1994). The marker dilution technique requires a volume of dye that may be proportionally larger than the small volume of feed given to premature infants, hence, is less suitable (Kelly & Newell, 1994; Newell et al., 1993). Although ultrasonography is a non-invasive technique, the validity of this test remains to be established. Studies with both techniques, however, show similar findings.

Studies have demonstrated little or no duodenal motor response to water and half-strength formula feeds. With full strength formula given by slow infusion, however, there was a sharp increase in motor activity (Baker & Berseth, 1997). A similar response was not elicited with bolus feeds of full strength formula as there was profound motor quiescence (Baker & Berseth, 1997). Similar results were not demonstrated in an earlier study (Currao, Cox, & Shapiro, 1988) which examined clinical outcomes, namely, residuals and time taken to reach an enteral energy intake of 100 Kcal/kg (418 Kjoul/kg). Infants in the half-strength group were found to have fewer residuals and reached the enteral energy intake of 100 Kcal/kg (418 Kjoul/kg) sooner (8.0 versus 11.0 days, p < 0.043). In this study, however, feeds were advanced at twice the volume per feeding in the half-strength formula group compared to the full-strength formula group.

Response of gastrointestinal peptides to formula and water feedings also differed. Plasma concentrations of gastrin, gastric inhibitory peptide, neurotensin, and peptide YY were significantly increased with formula feedings and remained unchanged with water
feedings (Berseth, Nordyke, Valdes, Furlow, & Go, 1992). In this study, premature infants were given enteral feedings intraduodenally.

Studies comparing infant response to feedings of premature infant formula or premature human milk, have shown rapid growth, as measured by weight gain, and increase in length and head circumference, in premature infants fed premature formula (Bell, Halliday, McClure, & Reid, 1986; Chan, Mileur, & Hansen, 1988; Modanlou, Lim, Hansen, & Sickles, 1986). These studies are not randomized controlled trials, hence, the results may not be valid as known prognostic factors and unknown determinants may be unequally distributed between comparison groups (Leasure & Allen, 1995). Randomization to premature human milk, however, is an ethical problem.

Svenningsen, Lindroth, and Lindquist (1982) conducted the only randomized controlled trial (n = 48) which compared premature human milk, which was mostly mother’s own milk, to standard energy formula with different protein content. The energy intake was isocaloric. This study showed no statistically significant difference in weight gain in the three groups. This study also evaluated neurodevelopmental outcome at 18 months and audiometric assessment at 10 to 14 months, and found similar results among infants in the 3 groups: premature human milk with 1.6 g protein per 100 Kcal, standard calorie formula with 2.3 g protein per 100 Kcal, and standard calorie formula with 3.0 g protein per 100 Kcal (Svenningsen et al., 1982). Svenningsen et al.’s study lacked sufficient power to detect differences in neurodevelopmental outcomes.

Although studies have shown that low birth weight infants fed premature formula
have better growth than those fed unfortified premature human milk, human milk may confer other nutritional and nonnutritional advantages (Schanler, Hurst, & Lau, 1999). Human milk is more easily digested and absorbed because of the organization of the fat globule, the pattern of fatty acids, the distribution of the triglyceride molecule, and the presence of bile salt-stimulated lipase (Schanler, 1995). Human milk is also thought to have a unique supply of certain essential fatty acids, namely, linoleic acid, linolenic acid, arachidonic acid (AA), and docosahexanoic acid (DHA) (Hay, 1996; Innis, 1999), which are important for membrane structure and function (Hay, 1996). Deficiencies in these essential fatty acids have been linked to deficits in neurological function such as visual acuity and learning (Hay, 1996).

Studies scrutinizing the role of these fatty acids in infant growth and development need to be interpreted with prudence (Innis, 1999) as more recent studies reveal that maternal diet (Connor, Lowensohn, & Hatcher, 1996) and gestational age (Foreman-van Drongelen et al., 1995) may affect fatty acid status at birth. Future studies need to consider these two factors when assessing the role of AA and DHA, found in human milk, in infant growth and development (Innis, 1999).

For premature infants neurodevelopmental outcomes are a concern (Schanler et al., 1999), and human milk may confer a developmental advantage (Hay, 1996). A multicenter randomized controlled trial showed that premature infants who received human milk during their hospitalization had a significantly higher intelligence quotient at 18 months of age (Lucas et al., 1990). This difference in intelligence quotient was also
evident at 7.5 to 8 years of age. At this time, a 8.3 point advantage, or over half a
standard deviation difference, in intelligent quotient remained. Adjustments were made
for factors, such as mother’s education and social class, which might have confounded this
comparison. A dose response relationship was found, that is, there was a relationship
between the proportion of mother’s milk in the diet and subsequent intelligent quotient

Human milk may have other protective roles (Schanler et al., 1999) as lower rate of
infection (Narayanan, Prakash, Bala, Verman, & Gujral, 1980; Schanler, 1995), and
incidence of NEC (Lucas & Cole, 1990; Yu, Jamieson, & Bajuk, 1981) are reported in
infants fed human milk. Human milk has host defense factors, such as Immunoglobulin A
and Immunoglobulin G (Schanler, 1995). Some host defense factors, such as
Immunoglobulin A, are excreted in feces suggesting that these factors may have a
protective role locally throughout the gastrointestinal system (Eibl, Wolf, Furnkranz, &
Rosenkranz, 1988; Schanler, Goldblum, Garza, & Goldman, 1986; Schanler et al., 1999).
Receptors are present on the intestine for host defense factors, such as Immunoglobulin G,
which suggests that there is a potential mechanism for the transport of these factors,
postnatally, from maternal milk to the infant (Israel, 1994).

Bifidobacteria, a gram-positive anaerobic bacteria, predominate in breast-fed infants
and may reduce the development of NEC in premature infants (Sakata, Yoshioka, &
Fujita, 1985). Bifidobacteria have the ability to reduce local luminal pH and prevent
growth of more pathogenic organisms such as Escherichia coli, hence, reduce the risk of

Human milk has been shown to contain high concentrations of growth factors. EGF is one of the major growth-promoting factors in human milk. These growth factors have been shown to promote growth of cultured cells (Read et al., 1984). EGF modulates secretion of gastric acid, hence, may play a role in protecting the gastrointestinal tract. The role of EGF in actual development is not known (Montgomery et al., 1999).

Steer et al. (1992) suggest that clinicians should utilize diets for premature infants which promote growth and nutrient accretion rates similar to intrauterine rates. Breast milk should be supplemented if the growth is poor. Over-enthusiastic supplementation should be avoided as, paradoxically, over supplementation (protein intakes > 6 g/kg per day) can result in impaired developmental outcomes (Goldman, Freudenthal, Holland, & Karelitz, 1969; Goldman, Goldman, Kaufman, & Liebman, 1974; Goldman, Liebman, Freudenthal, & Reuben, 1971; Steer et al., 1992).

In summary, based on the current state of knowledge, there is little evidence to support the use of dextrose or diluted formula in the nutrition management of VLBW infants. Studies comparing premature human milk and premature infant formula have focused on short-term outcomes, which may be of questionable significance given the lack of long-term follow-up. The use of breast milk seems to be the best feeding option, that is, type of feed. The CPG will advocate the use of expressed breast milk, however, if
breast milk is unavailable, either because the parents have decided not to breast feed or supply is limited, then VLBW infants will receive premature infant formula. Since the CPG conforms to what is standard practice in the NICU, the study will not monitor the type of feed infants are receiving.

3.2.5 Feeding advancement

Although "enteral feedings remain the ‘gold standard’ for providing optimum nutrition" (Buus-Frank & Adams, 1994, p. 1) to VLBW infants, the practical aspects of feeding can be complicated, for instance, feeding advancement. At present, there are no clear guidelines in the NICU with respect to feeding advancement. Data from a pilot study examining standard practice in the NICU, included in Appendix A, reveals that not only is there variability in feeding orders related to feeding advancement, there is some degree of discretion exercised by the nurse at the bedside. For instance, if the nurse reasoned that the increases ordered were too slow, then feedings were advanced more quickly. Although this pilot study focused on the first feeding order, it epitomizes the variability present in all subsequent feeding orders and the lack of clear guidelines for feeding advancement.

Feeding practices, more specifically, rapid increases in feeds (Goldman, 1980; Spritzer et al., 1988; Uauy et al., 1991) in stressed premature infants, put them at greater risk for developing NEC (Anderson & Kliegman, 1991; Kliegman & Fanaroff, 1984; McKeown et al., 1992; Zabielski et al., 1989). Differences in increments in feeding rate in studies comparing infants who developed NEC to infants who did not develop NEC, was
as large 40 to 60 cc/kg per day (Anderson & Kliegman, 1991; McKeown et al., 1992). Thureen and Hay (1993) concluded that there is not enough evidence to support that NEC is associated with increments in feeds. The authors, however, maintain that increments of < 20 cc/kg per day in feeding volume seem prudent.

Studies which showed an association between rapid increases in feedings and NEC (Anderson & Kliegman, 1991; Book, Herbst, & Jung, 1976; Covert, Neu, Elliott, Rea, & Gimotty, 1989; Goldman, 1980; McKeown et al., 1992; Spritzer et al., 1988) lack methodologic rigor and are weakened by retrospective analysis (e.g., Anderson & Kliegman, 1991; Covert et al., 1989; Goldman, 1980; McKeown et al., 1992). Study designs include chart reviews (e.g., Book et al., 1976; Spritzer et al., 1988), case-control (e.g., Anderson & Kliegman, 1991) and matched case control (e.g., McKeown et al., 1992). Other limitations of these studies include: (a) small sample size (e.g., Anderson & Kliegman 1991) had 19 cases and 36 control babies; (b) confounding variables such as differences in timing of first feeding (e.g., Covert et al., 1989), feeding methods between groups, and number of different formulas used during the period of data collection (e.g., Goldman, 1980); and (c) recall, surveillance and researcher bias (e.g., McKeown et al., 1992). Table 7 summarizes the characteristics of these studies.

Several studies have attempted to appraise the effect of different rates of advancement of enteral feedings on neonatal outcomes such as NEC, feeding intolerance, days to full feeds, days to regain birth weight, and days to discharge. A prospective randomized controlled trial comparing feeding increments of 10 cc/kg per day and 20
cc/kg per day failed to verify the trend toward greater incidence of NEC in infants receiving rapid feeding increments (Book et al., 1976). In two more recent prospective randomized controlled trials (Caple et al., 1997; Rayyis, Ambalavanan, Wright, & Carlo, 1999) no difference in the incidence of NEC was associated with rapid increments in feeds. "Slow" increments of feeds were defined as 20 cc/kg per day (Caple et al., 1997) or 15 cc/kg per day (Rayyis, et al., 1999), whereas "fast" increments of feeds were defined as 30 cc/kg per day (Caple et al., 1997) or 35 cc/kg per day (Rayyis et al., 1999).

The studies on feeding advancement differ in their characteristics which are summarized in Table 7. Weight ranges of infants admitted to the study were variable. Infants were < 1200 grams (Book et al., 1976), 1000 to 2000 grams (Caple et al., 1997), or 501 to 1500 grams (Rayyis et al., 1999). Rayyis et al.'s study was the only one that outlined the inclusion and exclusion criteria. Their study, however, included infants with IUGR which is most likely to have major effects on the development of the gastrointestinal system, particularly the small intestine (Avila, Harding, Rees, & Robinson, 1989). As a result, it is imperative that such confounding variables be either controlled by using stratified random sampling, or by establishing strict exclusion criteria (e.g., exclude infants with IUGR) or be measured to ensure equal distribution in the two groups being compared. Other confounding variables which may have an impact on the outcomes of interest and were not measured include timing of feeding (Caple et al., 1997), and method of feeding (Caple et al., 1997).

Convenience sampling was employed by Book et al.'s (1976) study. It is unclear
Table 7. Characteristics of Studies on Slow Versus Rapid Advances in Feeds

<table>
<thead>
<tr>
<th>Study</th>
<th>Anderson and Kliegman, 1991</th>
<th>Book et al., 1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Case control.</td>
<td>Randomized</td>
</tr>
<tr>
<td>n</td>
<td>57; Control=38; NEC=19</td>
<td>21; S=14; F=15</td>
</tr>
<tr>
<td>Subjects</td>
<td>Alimentation records of 19 patients who developed NEC were compared with 2 matched patients controlled for BW and time of admission.</td>
<td>Infants &lt; 1200 g.</td>
</tr>
<tr>
<td>Intervention</td>
<td>In S group volume was increased 10 cc/kg per day. In F group volume was increased 20 cc/kg per day. Intermittent gavage feeding method and 20 to 24 Kcal/oz cow milk formula used.</td>
<td>No significant difference in NEC, gastrointestinal problems (abdominal distension, diarrhea and frequent emesis).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Infants with NEC had: the greatest 1 day feed increment, a greater feed increment rate from initiation of feeds to day of maximum feed, and excessive fluid volumes (maximum TFI on day 5).</td>
<td>No significant difference in onset of feed between groups. No exclusion criteria. Feeding intolerance not defined. Management of feeding intolerance not described. No blinding of assessors.</td>
</tr>
<tr>
<td>Comments</td>
<td>Small sample size. Weak methodologic design. Criteria for diagnosis of NEC given.</td>
<td>Do not state how infants were randomized. Diagnosis of NEC based on both x-ray and clinical evidence (e.g. bleeding, emesis, abdominal distension). No significant difference in onset of feed between groups. No exclusion criteria. Feeding intolerance not defined. Management of feeding intolerance not described. No blinding of assessors.</td>
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</tbody>
</table>

Abbreviations: birth weight (BW); fast advances in feeds (F); necrotizing enterocolitis (NEC); slow advances in feeds (S); total fluid intake (TFI)
<table>
<thead>
<tr>
<th>Study</th>
<th>Caple et al., 1997</th>
<th>Covert et al., 1989</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized</td>
<td>Retrospective case control review</td>
</tr>
<tr>
<td>n</td>
<td>150; S=81; F=69</td>
<td>76; Control=38; NEC=38</td>
</tr>
<tr>
<td>Subjects</td>
<td>Premature infants.</td>
<td>Patients with NEC matched with control infants for BW and date of admission. Patients with congenital anomalies excluded.</td>
</tr>
<tr>
<td>Intervention</td>
<td>S = 20 cc/kg per day&lt;br&gt;F = 30 cc/kg per day&lt;br&gt;Both groups started at their respective volume and advanced daily by their assigned volume to a total fluid intake of 150 cc/kg per day. Fed either full strength formula or human milk.</td>
<td>No difference in maternal and perinatal characteristics. NEC patients had higher 5 minute Apgar score and less significant respiratory disease. NEC patients began feedings at an earlier age, reached full feedings at an early age and had a shorter interval between initiation of feedings and attainment of full feedings. Patients with early onset NEC (&lt; 21 days) had less significant respiratory disease and were fed more rapidly than late onset patients.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in incidence of NEC. Fast group regained BW faster, reached full calories sooner, had fewer days of intravenous fluids, and went home sooner (p&lt;0.05).</td>
<td>NEC defined using Bell Staging Criteria. Methodology - weak. 50% out born patients. Computer based program for data record. Unsure of learning curve and accuracy of data entry. Unable to locate medical records of two patients with NEC.</td>
</tr>
<tr>
<td>Comments</td>
<td>Abstract only. Do not state how infants were randomized and number different in each group. Do not state characteristics of participants. Unsure if caregivers and data collectors were blinded. Inclusion/exclusion criteria not stated. Feeding initiated as per attending's discretion, therefore, there may have been bias as do not state if there were differences between groups. Feeding intolerance not defined and management not described in 2 time periods.</td>
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Abbreviations: birth weight (BW); fast advances in feeds (F); necrotizing enterocolitis (NEC); slow advances in feeds (S)
<table>
<thead>
<tr>
<th>Study</th>
<th>Goldman, 1980</th>
<th>McKeown et al., 1992</th>
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<tr>
<td>Design</td>
<td>Retrospective case control</td>
<td>Matched case control</td>
</tr>
<tr>
<td>n</td>
<td>Control=?, NEC=26</td>
<td>118; Control=59; NEC=59</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants &lt;2500 g, 10% sample of all admissions were studied.</td>
<td>Patients who died or were diagnosed with NEC (1985-1989) were matched with control patients for race, BW and date of birth. Criteria applied to both groups: survival at least 24 hours, availability of complete records, absence of congenital anomalies and CNS defect.</td>
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**Intervention**

**Outcomes**
- Correlation found between the yearly incidence of NEC and percentage of infants in that year who had received large (40 or 60 cc/kg per day) increases in feeding volume. Seven NEC patients received > 150 cc/kg per day of formula prior to onset of NEC (large volumes implicated).
- NEC patients were fed earlier, received full strength formula sooner and received larger feeding volumes and increments. More highly stressed infants (risk index) were more vulnerable to larger feeding increments. Delayed feeding related to delayed onset of NEC.

**Comments**
- Weak methodology. Characteristics of infants with NEC included those who had received exchange transfusion, fed by various methods including nasojejunal and received 1 of 7 different formulas. Accuracy of records questionable.
- Weak methodology. Accuracy of records questionable. BW not categorized (e.g. infants < 1500 g), majority of patients < 2500 g. Identified cases based on diagnosis recorded by the attending neonatologist, excluded cases which did not fit Bell’s Modified Staging of NEC (stage 2 or higher). Clinician and surveillance bias.

Abbreviations: birth weight (BW); central nervous system (CNS); necrotizing enterocolitis (NEC)
Table 7. Characteristics of Studies on Slow Versus Rapid Advances in Feeds ... cont’d

<table>
<thead>
<tr>
<th>Study</th>
<th>Rayyis et al., 1999</th>
<th>Spritzer et al., 1988</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Randomized. Stratified into 4 BW groups.</td>
<td>Before and after introduction of a “cautious feeding regimen”</td>
</tr>
<tr>
<td>n</td>
<td>187; S=98; F=87</td>
<td>1466; Before (1980-1983)=686; After (1984-1987)=780</td>
</tr>
<tr>
<td>Subjects</td>
<td>Infants with BW 500-1500 g and gestational age ( \leq 34 ) weeks. Exclusion criteria: Apgar score ( &lt; 3 ) at 5 minutes, hemodynamic instability; life threatening malformation, polycythemia, exchange transfusion; breast milk feeding and multiple gestation of triplets or more.</td>
<td>Infants considered at risk for NEC. Infants ( &lt; 2000 ) g who did not have signs of NEC.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Slow feeders received 15 cc/kg per day increments. Fast feeders received 35 cc/kg per day increments. Fed Similac Special Care 20.</td>
<td>Before: first feed 20-40 cc/kg per day full strength formula, volume increased 20-40 cc/kg per day. After: first feed 20 cc/kg per day formula diluted with 5% dextrose, volume increased 20 cc/kg per day. Formula concentration increased gradually. High risk infants were NPO for 1 week.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>No significant difference in incidence of NEC (Bell ( \geq II )) and NEC with perforation. Fast feeding group achieved full feedings sooner and regained BW sooner. No significant difference in age at discharge.</td>
<td>In before time period 41 patients developed NEC. In after time period 5 infants developed NEC. Decrease did not coincide with the admission of more mature infants or infants with lesser problems as judged by need for ventilation and incidence of NEC.</td>
</tr>
<tr>
<td>Comments</td>
<td>Clinician decided when to initiate feeds and increased only if tolerated (residuals ( &lt; 20% )), hence, introduce bias. Do not state use of TPN or energy intake in both groups. Do describe how feeding intolerance was managed. Radiologist interpreting x-rays for NEC was blinded to group assignment.</td>
<td>Risk assessment based on “suffered ischemia of alimentary tract structures”, which was subjectively and objectively defined. Use of TPN in both groups not stated. TFI in both groups not stated. Do not give energy intake in both groups. Changes in resuscitation and ventilation strategies in the 2 time periods not described. Changes in use of indomethacin for treatment of PDA not described.</td>
</tr>
</tbody>
</table>

**Abbreviations:** birth weight (BW); fast advances in feeds (F); necrotizing enterocolitis (NEC); nothing by mouth (NPO); patent ductus arteriosus (PDA); slow advances in feeds (S); total fluid intake (TFI); total parental nutrition (TPN) ........................... cont’d
how Caple et al. (1997) determined a sample size of 150. It is also unclear how infants were randomized given the different number of infants in each group, 81 in the slow increment group versus 69 in the fast increment group. Although a sample size was calculated by Rayyis et al. (1999), the incidence of NEC was different during the study period and the authors acknowledge this limitation in the discussion. In all three studies, infants were randomized to either the slow or fast increments in feeds. The method of randomization, block randomization according to weight stratification, was described in only one study (Rayyis et al., 1999).

All three studies defined NEC, whereas only one study (Rayyis et al., 1999) addressed unequivocally the issue of evaluator bias of the radiologist interpreting radiographic evidence of NEC. In this study a radiologist, independent of the study, interpreted the x-rays, thereby blinding the observer to the group assignment of the infant. Inter-observer variation, and diagnostic surveillance bias because of care giver bias of monitoring infants in the fast increment group more closely, were not addressed by any of the studies. While data on signs and symptoms of NEC were collected, such as bloody stools (e.g., Caple et al., 1997) and feeding intolerance, it was not always certain what constituted feeding intolerance, and how this was managed. Additionally, some studies failed to collect data on variables related to feeding intolerance such as number of interruptions of feeds (e.g., Book et al., 1976; Caple et al., 1997; Rayyis et al., 1999), and days to full feeds (e.g., Book et al., 1976).

A systematic review undertaken by Kennedy and Tyson (1998) included the above
three randomized or quasi-randomized trials (Book et al., 1976; Caple et al., 1997; Rayyis et al., 1997). An overall reduction in days to full enteral feeding (weighted mean difference = -3.2 days) and days to regain birth weight (weighted mean difference = -2.1 days) was noted amongst infants in the rapid rate of feeding advancement group. There was no significant effect on NEC (relative risk = 0.9, 95% confidence interval = 0.46 to 1.77) or length of hospital stay (weighted mean difference = -3.8 days; 95% confidence interval = -9.1, 1.5).

Methodological quality of the included studies were assessed to be “good” by Kennedy and Tyson (1998) based on concealment of group assignment at randomization, blinding of radiologist confirming the diagnosis of NEC, and inclusion of all randomized infants in the analyses (p. 3). Kennedy and Tyson (1998) concluded that the ideal rates of advancement remains unclear especially for extremely low birth weight infants because studies included in the systematic review had different birth weight ranges, and different rates of advancement in feedings. As well, although more rapid advancement of feedings may be advantageous with respect to shorter time to regain birth weight and shorter time to achieve full feeds, information regarding safety (incidence of NEC) and the effect on length of hospital stay seem unclear because of broad confidence intervals (Kennedy & Tyson, 1998).

In summary, in the CPG feeding advancement will not exceed approximately 30 cc/kg per day as this seems to be the most conservative estimate of what is considered rapid advancement. Moreover, this value is below the 40 to 60 cc/kg per day difference
in increments in feeding rate noted in infants who developed NEC in studies comparing
infants who developed NEC to infants who did not develop NEC (Anderson & Kliegman,
1991; McKeown et al., 1992). To determine the safety of this approach in feeding
advancement in VLBW, this study will compare the incidence of NEC between the
Standard Practice group and the CPG group. To determine the efficacy of this
approach, this study will measure variables related to feeding intolerance including
number of feeding interruptions, days on TPN, and days to full feeds, as well, days to
regain birth weight, and days to discharge. Infants who are IUGR will be excluded from
this study given that the development of the gastrointestinal system, particularly, the
small intestine, may be altered in these infants (Avila et al., 1989).

3.2.6 Feeding intolerance: definition and management

One can surmise from the discussion of gastrointestinal ontogeny, in Chapter 2, that
neuromuscular development occurs early in gestation, however, normal patterns of
contractile activity do not occur until after birth. Functional limitations of the premature
infants’ gastrointestinal system hinders successful feeding as these infants develop feeding
intolerance. Delayed gastric emptying in premature infants frequently presents as failure
to tolerate enteral feeds or feeding intolerance (Kelly & Newell, 1994). According to
Berseth and Nordyke (1992), feeding intolerance reflects a delay in the maturation of the
neonate’s motor activity in the gut as these infants do not have complete interdigestive
cycles during fasting. Additionally, these infants are not able to change their pattern of
motor activity in response to feeds. Although this lack of fed response is transient, it can
take 4 weeks to resolve (Berseth & Nordsyke, 1992).

Intestinal motor activity is important for the movement of food down the gastrointestinal tract (Berseth, 1992). Inability to efficiently expel waste products can lead to a sequence of events. First, bacteria can proliferate (Snapp, 1994). These bacteria and their toxins can adhere and cross into the intestinal lining cells and/or the systemic circulation (Israel, 1994) because the premature infant’s intestinal barrier is immature (Israel, 1994). Second, undigested carbohydrates can ferment leading to progressive organic acid production which can then destroy the mucosal barrier (Snapp, 1994). These events can lead to mucosal disruption which increases permeability, of the already immature intestinal barrier, to antigens, bacteria, viruses and toxins leading to an inflammatory cascade response known as NEC (Israel, 1994; Snapp, 1994).

The cause of NEC, however, remains unclear and risk factors include prematurity, feeding, intestinal ischemia, and bacterial colonization (Kliegman, 1990). Manifestation of NEC include abdominal distention, residuals, vomiting, bloody stools, metabolic acidosis, cellular destruction, and gut necrosis. Hallmarks of NEC include pneumatosis intestinalis, hepatic portal venous gas, perforation and pneumoperitoneum; these are evident on abdominal x-ray (Meerstadt & Gyll, 1994; Snapp, 1994). According to a study done by Uauy et al. (1991) to characterize the biodemographic and clinical correlates of NEC in VLBW, there was a 10.1% overall prevalence of proven NEC (Bell stage II and beyond) and an additional 17.2% prevalence of suspected NEC (stage I). Appendix C describes the classification of NEC. In this study, the mortality rate was 54% for VLBW infants
with stage III NEC (Uauy et al., 1991).

Through a retrospective chart audit in a 33-bed NICU in a university affiliated teaching hospital, the incidence of feeding intolerance was 63% in infants whose gestational age was 26 to 32 weeks (Premji & Wilson, 1994, unpublished report). Data for the incidence of NEC in this unit are unavailable. Prevalence of NEC varies greatly among centers and is thought to relate to early clinical practices of neonatal care (Uauy et al., 1991). Consequently, feeding intolerance is a significant clinical dilemma when considering nutritional management for infants < 1500 grams. At present, each clinician defines feeding intolerance based on their individual knowledge and expertise. Modified Bell staging criteria is used for classification of NEC (see Appendix C). Management of NEC is based on this staging criteria.

Generally speaking, there is agreement in the literature that the signs of feeding intolerance include residuals, abdominal distention, and spitting up. There is, however, no consensus in the literature with regard to the operational definition of feeding intolerance. Researchers have tried to operationalize the definition by quantifying the various signs of feeding intolerance. For example, Slagle and Gross (1988) defined feeding intolerance as:

"... emesis, bile-stained gastric residuum, or marked abdominal distention (> 2 cm increase in abdominal girth). Small (< 2 ml) nonbilious gastric residuum was refed. During the advancement phase, feedings were not increased if the total gastric residuum from the previous day was > 10% of the feeding. A diagnosis of NEC was made if clinical signs of feeding intolerance occurred in association with pneumatosis intestinalis on abdominal radiograph." (p. 527).

Various themes of this definition exist in the literature (Berseth & Nordyke, 1992; Dunn et
al., 1988; Ostertag et al., 1986; Rayyis et al., 1999; Robertson & Bhatia, 1993; Troche et al., 1995) and, in some instances, the definitions have included guidelines for management.

For example, Berseth and Nordyke (1992) stated:

"Feeding intolerance was defined as vomiting, an increase in abdominal girth by more than 1.5 cm, or milk retained in the stomach 2 hours after the feeding infusion had been completed. For a single episode of vomiting, feedings were withheld 4 to 8 hours. For increased abdominal girth, feedings were withheld until the abdominal girth decreased to baseline fasting girth. For milk retained in the stomach, feedings were withheld for an additional 2 hours. If no milk remained in the stomach at the end of the additional 2 hours, the next feeding was given. If milk was still present at the end of this additional 2 hours, feedings were withheld, and the presence of milk was reassessed every 2 hours. If milk was still present after an additional 4 hours, feedings were withheld for 24 hours." (p. 1524).

The lack of consensus in the literature about the operational definition of feeding intolerance is reflected in practice, as strategies used to manage feeding intolerance are inconsistent.

Standard practice for the management of feeding intolerance included, decreasing the volume of feed and/or increasing the time interval between feeds, or holding feeds. The number of days feeds are held is dependent upon the clinical status of the infant, the number of episodes of feeding intolerance, x-ray findings if available, and the clinician's level of comfort with managing feeding issues. Prokinetic agents, such as erythromycin and cisapride, are also prescribed for persistent problems with feeding intolerance (see Appendix A).

Literature appraising various strategies for the management of feeding intolerance have focused on gastric emptying and/or intestinal transit. As previously discussed,
dietary factors are known to affect gastric emptying. Kelly and Newell (1994) suggest that alteration in the composition of milk may offer an avenue for promoting gastric emptying and consequently feeding tolerance for premature infants. However, a systematic approach to altering milk composition has not been explicated or tested in practice.

Hyperglycemia affects gastric emptying in adult patients (Hebbard, Samsom, Sun, Dent, & Horowitz, 1996; Horowitz, Wishart, Jones, & Hebbard, 1996; MacGregor, Gueller, Watts, & Meyer, 1976; Oster-Jorgensen, Pedersen, & Larsen, 1990; Schvarcz et al., 1997). Even changes in blood glucose within the physiologic range altered gastric emptying. More specifically, physiologic hyperglycemia (glucose concentration of 8 mmol/L) resulted in decreased gastric emptying of both solid and liquid meals, in normal adults and adults with insulin-dependent diabetes mellitus (Schvarcz et al., 1997). The underlying mechanism of this influence has not been explicated (Schvarcz et al., 1997; Hebbard et al., 1996), however, it is felt that both neural and humoral mechanisms may be important (Schvarcz et al., 1997). One may be able to modulate gastric emptying by altering blood glucose concentration through tailoring of dextrose concentration in TPN, dietary intake, or pharmacological means such as initiation of insulin. However, a better understanding of the pathophysiology of blood glucose concentration and its effect on gastric emptying is necessary before such strategies are implemented.

MEN may be beneficial for those infants who exhibit an immature intestinal contractile activity as feeding promotes maturity of motor activity (Dumont & Rudolph,
1994). As early as 25 weeks gestation, infants responded to enteral nutrition, that is, feeds stimulated the development of motility patterns similar to those seen in term infants (Berseth, 1990). However, there was still presence of immaturity in fasting motor activity [MMC]. Fasting motor activity contributes considerably to the movement of food down the gastrointestinal tract (Berseth, 1990), hence, infants may experience problems with residuals. In order to conform to the immaturity of the fasting motor activity [MMC], Berseth (1990) suggests adjusting feeding intervals, that is, giving less frequent feedings until the MMC becomes more coordinated.

Prokinetic agents which alter the natural progression of maturation of the MMC, such as erythromycin and cisapride, may be therapeutic for infants experiencing feeding intolerance. Although the role of cisapride in enhancing gastric motility is well supported (Hyman, McDiarmid, Napolitano, Abrams, & Tomomasa, 1988; Van Peer, Woestenborghs, Verlinden, Meuldermans, & Heykants, 1986; Vandenplas, Sacre, & Loeb, 1986), there is a paucity of literature with regards to its efficacy in reducing feeding intolerance in VLBW. Additionally, concerns raised about the safety of cisapride use in the VLBW, particularly the occurrence of prolonged QT interval, has prompted Janssen-Ortho Inc., the manufacturers of cisapride, to release safety information prohibiting the use of cisapride in premature infants (Premji & Paes, 1999). A review of the literature examining the efficacy and safety of cisapride use in VLBW infants, written by the author and colleagues, is included in Appendix B.

Erythromycin has recently emerged as a potential prokinetic agent if given in doses
substantially lower, 1 to 3 mg/kg per dose, than the commonly used antimicrobial dose (Weber, Richards, & McCallum, 1993). Low dose erythromycin acts as a motilin agonist and induces premature MMC activity (Weber et al., 1993) in premature infants (Tomomasa, Miyazaki, Koizumi, & Kuroume, 1993). Low dose erythromycin, also stimulates coordinated antroduodenal contractile activity which may be beneficial in promoting gastric emptying (Janssens et al., 1990; Otterson & Sarna, 1990). In four infants, 31 to 40 weeks gestation, who presented with continuing large volume bile stained nasogastric aspirates, that is severe intestinal dysmotility, following gastrointestinal surgery, striking improvement was noted after commencing erythromycin (12 mg/kg) treatment. These infants were able to be established on full bottle feeds three weeks after starting treatment (Simkiss, Adams, Myrdal, & Booth, 1994). Gastrointestinal side effects of erythromycin include nausea, vomiting, abdominal cramping, diarrhea, and arrhythmias (Tomomasa et al., 1993; Weber et al., 1993) and it use in clinical practice should be weighed against possible adverse side-effects (Zara, Qin, Pilot, Thomson, & Maskell, 1987). These gastrointestinal side effects may not pertain to low dose erythromycin. There is also uncertainty about the effects of low dose erythromycin on: an infant’s established normal bacterial flora, development of pathogens resistant to antibiotics, and incidence and type of nosocomial infections in the NICU setting (Premji & Paes, 1999). The efficacy and safety of the use of low dose erythromycin in VLBW infants has not been established.

*In summary, given the lack of agreement in the literature with regard to the*
operational definition of feeding intolerance and its management, consensus decision-making will be employed to embrace a definition of feeding intolerance and identify strategies for its management. During consensus decision-making, consideration will be given to the literature appraising management of feeding intolerance. Variables related to feeding intolerance including number of feeding interruptions, days on TPN, and days to full feeds, will be measured in this study. Additionally, days to regain birth weight, days to discharge, and incidence of NEC and sepsis will also be measured to assess the efficacy and safety of the strategies related to management of feeding intolerance. This study will monitor the use of prokinetic agents such as erythromycin and cisapride to ensure that the efficacy of this study is related to the CPG.

3.2.7 Nursing management of enteral tube feedings

The participation of neonatal nurses is critical for the nutritional management of small premature infants. Neonatal nurses spend a great deal of time feeding, handling, and observing behavioral changes of the infant prefeeds, during feeds, and postfeeds. Neonatal nurses identify and solve problems related to regurgitation, abdominal distention, and residuals. Each nurse uses his/her individual expertise to solve these problems (Bragdon, 1983). The practice of withdrawing previous feeds for the purpose of checking tube placement and/or estimating gastric residuals illustrates the variation in nursing practice, particularly, nurse's management of feeding problems.

A small study done by Hodges and Vincent (1993) showed that the practice of withdrawing feeding was not universal, however, a large percentage (96%) of neonatal
nurses checked gastric residuals prior to each gavage feeding. The management of feeding residuals was variable and included: (a) refeeding at each feeding (4%); (b) refeeding at most feedings (4%); (c) refeeding about ½ the time (0%); (d) refeeding < ½ the time (3%); (e) almost never refeeding (61.5%); and (f) never refeeding (19%) (Hodges & Vincent, 1993). Reasons cited for not refeeding gastric residuals were: (a) doctors do not order refeeding; (b) against hospital policy; (c) no literature demonstrating value of refeeding; (d) might be bad for infant; (e) unaware of proper procedure; (f) residual consisted of mucus and/or bile; and (g) residual < 20 percent of feeding order (Hodges & Vincent, 1993). Reasons for refeeding gastric residuals included: (a) the infant will benefit from the fluid, electrolytes, and enzymes in residuals; (b) the doctor ordered refeeding; (c) the literature demonstrates the value of refeeding; (d) residual consisted of milk; (e) residual > 50% of feeding ordered; and (f) residual contained medication (Hodges & Vincent, 1993).

A review of the nursing literature verified that there are no randomized controlled trials on the practice of checking for feeding residuals or management of feeding residuals. Certain recommendations have been made, based on the current knowledge, regarding the development of the gastrointestinal system. These recommendations include checking for gastric residuals prior to each gavage feeding and refeeding residuals. There is consensus among these authors (Bragdon, 1983; Flynn, Norton, & Fisher, 1987; Konstantinides & Shronts, 1983) that gastric residuals contain gastric acid and enzymes which buffer the infant's gastrointestinal system. Additionally, these residuals contain fluid and electrolytes.
Consequently, if these residuals are discarded, electrolyte imbalance and metabolic complications may ensue (Bragdon, 1983; Flynn et al., 1987; Konstantinides & Shronts, 1983), but have not been documented in studies.

At present, the nurse assesses the infant's tolerance to feeds and discusses the assessment with the clinician responsible for the medical care of the infant. Collectively, certain strategies and plans are implemented based on knowledge base, expertise, and level of comfort. These strategies and plans are modified based on the clinical progress of the infant, ongoing nursing assessment, and the clinician's discretion. Consequently, a multitude of approaches are taken to manage feeding intolerance which leads to inconsistency and sometimes confusion in the provision of care. It is imperative that decisions related to feeding problems be approached in a systematic way, as well, be based on current knowledge and research as the nutritional management of premature infants in the early weeks of life has an impact on later growth and development (Lucas, 1990; Morley & Lucas, 1993; Steer et al., 1992).

In summary, given the varied approaches taken by nurses in the management of feeding intolerance, CPG will outline, in figure format, parameters for nurses to follow for reaching a decision about managing gastric residuals and holding feeds. These parameters will be based on consensus decision-making as a research based approach can not be extrapolated from current research investigating strategies for the management of feeding intolerance.

To verify the efficacy of the strategies adopted for the management of feeding
intolerance, variables related to feeding intolerance including number of feeding interruptions, days on TPN, and days to full feeds will be measured. Secondary outcomes such as days to regain birth weight and days to discharge will also be assessed. Additionally, adverse effects, such as NEC and sepsis will be monitored to assess the safety of the strategies adopted for management of feeding intolerance. To ensure that differences in outcomes are related to the CPG, this study will also monitor the use of prokinetic agents such as erythromycin and cisapride.

3.3 Conclusion

Although infant nutrition remains the most widely researched area in pediatrics, there is a great deal of uncertainty in feeding small premature infants (Lucas, 1990). The uncertainty stems from the fact that there are a number of limitations to the research which potentially could affect the outcomes examined. First, most studies have focused on short-term outcomes (i.e., short-term growth). Second, studies have not rigorously controlled for confounding variables such as use of indomethacin for closure of PDA. Third, the studies have methodological limitations such as small sample sizes. Consequently, the body of research in the area of feeding small premature infants is plagued by inconsistent and controversial findings (Buus-Frank & Adams, 1994) which leads to great variation in practice.
Chapter 4

Clinical Practice Guidelines

4.1 Introduction

CPG are one strategy to address the challenges of feeding small premature infants. The underlying assumption in the development of CPG is that the evidence is unread or undigested, and that there is too much variation in practice. CPG attempt to “refine decision making and to narrow practice variation to a degree unlikely to be achieved ‘naturally’ by the target audience(s).” (Lewis, 1995, p. 1074). The literature stipulates a myriad of purposes for CPG, however, “the most frequently stated purpose ... is the synthesis of evidence-based medical decision making to reduce inappropriate variation in clinical practice patterns” (Merritt, Palmer, Bergman, & Shiono, 1997, p. 102). Additionally, the guidelines will assist practitioners, both medical and nursing, with limited clinical experience to make decisions about appropriate care for nutritional management of VLBW infants.

CPG are based on the philosophy of utilitarianism, that is, they exist to be useful (Lewis, 1995). Terms such as practice parameters, care maps, critical pathways, “neomaps”, and “neopaths” are used to denote CPG in general, or refer to specific varieties of CPG. CPG are becoming prevalent in neonatology and range from management of the infant at delivery (resuscitation), management of respiratory distress
syndrome and coordinating discharge from the NICU (Merritt et al., 1997). The use of CPG is being promulgated by a variety of organizations including physician associations (i.e., American Academy of Pediatrics), specialty societies (i.e., Centers for Disease Control, and Prevention and National Institutes of Health), local institutions, and governments (i.e., World Health Organization, and Agency for Health Care Policy and Research) (Battista & Hodge, 1995; Merritt et al., 1997).

Both medical and nursing care are covered in CPG (Clarke, 1996). CPG “provide an important resource for carrying out nursing responsibilities” (Clarke, 1996, p. 13). CPG can consist of a single statement, however, more typically, they are issued in sets of statements that relate to specific conditions or patient problems (Dracup, 1996).

4.2 Development of Guidelines

CPG for the nutritional management of premature infants < 1500 grams will integrate both medical and nursing care. These CPG will consist of statements directing clinicians about various areas related to the nutritional management of this population of infants. Given the current state of scientific knowledge, consensus decision-making was employed to develop CPG for certain areas of nutritional management of VLBW, namely initiation and duration of MEN, and definition and management of feeding intolerance.

4.2.1 Consensus decision-making process

Members of the neonatal gastrointestinal motility research group (NGMRG), including neonatologist, neonatal fellow, pediatric gastroenterologist, clinical nurse specialist/neonatal practitioner (CNS/NP), nutritionist, and pharmacist, were involved in
the development of the guidelines. A small subgroup of this local panel, which included the author, undertook an integrated review of the literature to develop the CPG for infants < 1500 grams. The local representation increased the probability of producing evidence-based guidelines (Lewis, 1995). Although, the values inherent in attitudes toward evidence, interpretations of the scientific research and consensus oriented conclusions may have played an important role in the development of the CPG, whenever possible, certain standard or established practices were also incorporated.

The CPG for feeding premature infants < 1500 grams were stratified into 3 weight categories: infants < 750 grams, infants ≥ 750 and < 1000 grams, and infants ≥ 1000 grams and < 1500 grams (see Tables 8, 9, 10 respectively). Infants were stratified into these 3 weight categories for a number of reasons. First, the gastrointestinal system would be at various stages of development, hence, stratification would allow for inclusion of strategies appropriate for a more narrow range of development. For example, infants approaching 1500 grams would have a more mature gastrointestinal system, as a result, one could be more aggressive in feeding these infants, that is, initiate earlier nutritional feedings, as well, advance feedings more rapidly (closer to the 30 cc/kg per day maximum). Second, standard practice varied considerably for infants toward the lower end and upper end of the spectrum of 1500 grams. Stratifying infants into these 3 weight categories would be consistent with present practice in the unit. Lastly, stratification allowed for more specific guidelines to be developed. For instance, rather than stipulating a rate of increase of feeding based on weight (i.e., 30 cc/kg per day), the guidelines would
<table>
<thead>
<tr>
<th>Trophic feeds:</th>
<th></th>
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<tbody>
<tr>
<td>Timing</td>
<td>start at 48 hours of life and continue for 48 to 72 hours</td>
</tr>
<tr>
<td>Route</td>
<td>indwelling nasogastric tube</td>
</tr>
<tr>
<td>Type of feed</td>
<td>full strength EBM or SMA Preemie 24</td>
</tr>
<tr>
<td>Amount and Frequency</td>
<td>1 cc every 4 hours (equals approximately 12 cc/kg per day for a 500 gram infant)</td>
</tr>
<tr>
<td>Increase in feeds</td>
<td>none</td>
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<tr>
<th>Nutritional feeds:</th>
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<tbody>
<tr>
<td>Timing</td>
<td>day 5 to 6 of life</td>
</tr>
<tr>
<td>Route</td>
<td>indwelling nasogastric tube</td>
</tr>
<tr>
<td>Type of feed</td>
<td>full strength EBM or SMA Preemie 24</td>
</tr>
<tr>
<td>Amount and Frequency</td>
<td>1 cc every 2 hours (equals an increase, from trophic feeds, of 12 cc/kg per day for a 500 gram infant)</td>
</tr>
<tr>
<td>Increase in feeds</td>
<td>1 cc every 24 hours; continue same increase until at full feeds (equals approximately 24 cc/kg per day increase for a 500 gram infant)</td>
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Abbreviations: expressed breast milk (EBM)
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<th>Trophic feeds:</th>
<th>Nutritional feeds:</th>
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<tr>
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<td><strong>Type of feed</strong></td>
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<tr>
<td>full strength EBM or SMA Preemie 24</td>
<td>full strength EBM or SMA Preemie 24</td>
</tr>
<tr>
<td><strong>Amount and Frequency</strong></td>
<td><strong>Amount and Frequency</strong></td>
</tr>
<tr>
<td>1 cc every 2 hours (equals approximately 16 cc/kg per day for a 750 gram infant)</td>
<td>2 cc every 2 hours (equals an increase, from trophic feeds, of 16 cc/kg per day for a 750 gram infant)</td>
</tr>
<tr>
<td><strong>Increase in feeds</strong></td>
<td><strong>Increase in feeds</strong></td>
</tr>
<tr>
<td>none</td>
<td>1 cc every 24 hours (equals an increase of 16 cc/kg per day for 750 gram infant)</td>
</tr>
<tr>
<td>If tolerates this for 48 hours, then increase 1 cc every 12 hours (equals approximately 32 cc/kg per day increase for a 750 gram infant)</td>
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**Abbreviations:** expressed breast milk (EBM)
Table 10. Feeding Practice Guidelines for Infants in the ≥ 1000 grams and < 1500 grams Category

<table>
<thead>
<tr>
<th>Nutritional feeds:</th>
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<tbody>
<tr>
<td>Timing</td>
<td>at 48 hours of life</td>
</tr>
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<td>Route</td>
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</tr>
<tr>
<td>Type of feed</td>
<td>full strength EBM or SMA Preemie 24</td>
</tr>
<tr>
<td>Amount and Frequency</td>
<td>1 cc every 2 hours (equals 12 cc/kg per day for a 1000 gram infant)</td>
</tr>
<tr>
<td>Increase in feeds</td>
<td>1 cc every 12 hours (equals an increase of 18 cc/kg per day for a 1000 gram infant)</td>
</tr>
</tbody>
</table>

Abbreviations: expressed breast milk (EBM)
state the actual increase of feeding (i.e., increase 2 cc every 2 hours).

Based on the current understanding of gastrointestinal ontogeny and review of the literature related the timing of feedings, it was concluded that MEN would be integrated as a strategy in the CPG. One could not extrapolate from this literature review the optimum timing of MEN because in some studies MEN was started as early as the first day of life and in other studies it was started as late as eighth day of life. Additionally, the MEN protocol varied in duration in these studies, ranging from 4 to 10 days. The NGMRG decided that MEN should be initiated soon after birth given the adverse effect of fasting on the gastrointestinal system. MEN would not be initiated as early as the first day of life but rather started at 48 hours of life as the clinicians had only recently been getting comfortable with starting enteral feedings in the first week of life. Additionally, it was felt that there would be great resistance to starting feeds on the first day of life because of concern regarding respiratory and cardiovascular stability particularly for infants < 750 grams. The 48 hours would allow the clinician to assess the stability of the infant and become comfortable with initiating feeds. Nutritional feeds would commence on Day 5 to 6 of life, as was the current practice. The exception was infants ≥ 1000 grams and < 1500 grams, as it was felt that these infants would tolerate nutritional feeds earlier. As a result, these infants would not receive MEN but rather start nutritional feeds at 48 hours of life (see Table 10).

The definition of feeding intolerance and strategies for its management embraced by the NGMRG for the CPG is outlined in Figure 1. Reasons for not following the CPG are
Feeding Practice Guidelines Should Not Be Followed If:
- Apgar score is ≤ 3 at 5 minutes of age
- Infant is on indomethacin
- Attending physician is not in agreement

Decision regarding gastric aspirates and holding feeds when infant is on induction feeds
Hold feeds and ask MD or CNS/NP to assess infant if:
- Residuals regardless of amount contain bile or blood.
- Large amounts of residuals for greater than 24 hours.
- Clinical exam is abnormal.**

Decision regarding gastric aspirates and holding feeds when infant is on nutritional feeds
Every Feed

Check abdomen and Aspirate (% of previous feed left)

- If residuals < 50%, refeed aspirate along with formula or EBM to make up prescribed feed volume. If residuals persist for 2 feedings then contact MD or CNS/NP.
- If residuals > 50% or 1cc, which ever is greater, discard aspirate and do not feed. Assess abdomen.
- If residuals regardless of amount contains bile or blood. HOLD FEED. Ask MD or CNS/NP to assess infant.

Normal exam.* Reassess prior to next feed and feed prescribed volume. If 2 consecutive feeds held or 3 feeds held in 12 hour period, contact MD or CNS/NP.

Abnormal exam** contact MD or CNS/NP

---

# Mucus contains essential factors, hence, include in residual volume.
* Normal examination includes soft distention and/or visible bowel loops. If in doubt consult MD or CNS/NP.
** Abnormal examination includes tense distended abdomen, deep discoloration, enlarged bowel loops and/or no bowel sounds.

IN 24 HOUR PERIOD, if emesis > 50% of a previous feeding (based on your best estimate) on > 2 occasions, contact MD or CNS/NP to assess infant.

**Figure 1. Parameters for nurses to follow for decision regarding management of gastric aspirates and holding feeds.**

Abbreviations: physician (MD); clinical nurse specialist/neonatal practitioner (CNS/NP); expressed breast milk (EBM)
stipulated at the beginning of this figure. These reasons were based on the review of the literature examining gastrointestinal ontogeny and various areas of nutritional management discussed in Chapter 2 and Chapter 3, respectively.

Consideration was given to ease of calculating percent of residuals, for example, it would be easier to determine if the gastric aspirate is 50% of a feed, as opposed to 20% or 30% of a feed, when deciding on the operational definition of feeding intolerance. As well, consideration was given to nursing practice. Nutrition management is within the realm of nursing practice and it is important that nurses have autonomy with regard to decision making, particularly around issues concerning management of gastric aspirates and holding feeds. The CPG were developed such that nurses could practice independently, however, certain parameters were stipulated where the nurse would have to consult the physician or CNS/NP (see Figure 1). These parameters were based on clinical manifestation of NEC which includes abdominal distention, residuals, vomiting, bloody stools (Snapp, 1994), and clinical manifestation of bowel obstruction which includes bilious residuals and bloody aspirates.

Because of the lack of bedside nursing representation on the panel involved in developing the guidelines, nurses might have viewed the guidelines as a threat to their autonomy and felt that the guidelines were unnecessarily or inappropriately replacing their clinical judgment (Mittman, Tonesk, & Jacobson, 1992). The two CNS/NPs on the panel represented bedside nurses and attempted to ensure that the CPG took into consideration the interests of the bedside nurse. The CNS/NPs on the panel attempted to provide

The CPG were reviewed by the NGMRG, as well as other neonatal staff, both nursing and medical. Inservices were presented to elicit feedback regarding the guidelines and a recorder made notes of all feedback. The regular weekly educational session was used to present the guidelines to the neonatologists, neonatal fellows, residents, and CNS/NPs. These sessions are open to all neonatal staff including nursing staff. Since these sessions are infrequently attended by the transport team members, resource nurses, and bedside nurses, special inservices were arranged for the nurses. The initial inservice was video taped so that staff who worked only night shifts were able to access the information and offer their feedback on paper.

The feedback was appraised by the NGMRG and based on group consensus, the guidelines were finalized. The subsequent chapter explains the various strategies, with the underlying research and theoretical framework, used for dissemination, diffusion and implementation of CPG. Adoption of CPG has consequences for VLBW infants.

Guidelines should improve the nutritional outcomes of small premature infants. There is little evidence about the effectiveness of CPG in a NICU setting, therefore, evaluation of the implementation of such a clinical policy was undertaken. The subsequent chapter also explicates the methodology employed to study the efficacy and safety of these guidelines.
Chapter 5

Methodology

5.1 Introduction

The strategies aimed at dissemination, diffusion and implementation of CPG are reviewed in section 5.2. To support the strategies utilized, the theoretical framework which influenced the development of these strategies accompanies the discussion. Sections 5.3 to 5.9 of this chapter describe the setting, design, inclusion and exclusion criteria, data collection, sample size justification, statistical analysis, and plan for protection of subject’s rights.

5.2 Dissemination, Diffusion and Implementation of CPG

The neonatologists, neonatal fellows, and CNS/NPs were closely involved in the development of the CPG and were amiable to implementing these guidelines in practice. As a result, strategies aimed at dissemination, diffusion and implementation of CPG were directed at the nursing staff (see Figure 2). The following section elucidates the various strategies, and the underlying research and theoretical framework which guided the development of these strategies.

5.2.1 Dissemination

The outcomes of this study would only be meaningful if nurses complied with the CPG, particularly since feeding orders were not followed in 14 to 37% of the cases in the
Figure 2. Strategies directed at nursing staff aimed at dissemination, diffusion, and implementation of CPG.

Abbreviations: clinical nurse specialist/neonatal practitioner (CNS/NP); clinical practice guidelines (CPG)
pilot study done to delineate standard practice (see Appendix A). Lomas (1991) evaluated 19 studies that examined the impact of CPG on behaviour, and concluded that “the appraisal yields a pessimistic conclusion ... in most cases the words do not translate into action” (p. 43). Awareness of CPG was variable and ranged from 30 to 60% (Abelson & Lomas, 1990; Hill, Levine, & Whelton, 1988). Literature focusing on use of nursing practice research reveals similar findings. Variability among nurses in awareness of nursing research was seen, and awareness did not imply adoption of research in practice (Armitage, 1990; Brett, 1987; Coyle & Sokop, 1990; Kirchhoff, 1982; Michel & Sneed, 1995). Although CPG may not directly and immediately lead to adoption of the recommended behavior change, it does create awareness, which is an important achievement (Rogers, 1995).

Awareness represents the first stage of behavior change, which starts with predisposing or priming activities, and that triggers consideration of behavior change (Lomas, 1991). "Dissemination strategies comprise educational processes which aim to influence targeted groups' awareness, knowledge and attitudes of guidelines and their recommendations" (Grimshaw & Hutchinson, 1995, p. 913). Dissemination activities, therefore, are considered predisposing activities. Dissemination is an active concept and is an effective form of communication. This concept implies that there is an aggressive flow of information, and targeting and tailoring of information for the intended audience (Lomas, 1993). Various strategies, alone or in combination, have been used to disseminate CPG. These strategies include, but are not limited to, providing clinical
preceptorship, auditing practices and giving feedback, sponsoring local consensus processes, and marketing. Typically, few resources are allocated to dissemination of guidelines (Carter et al., 1995).

In order to disseminate the CPG for feeding premature infants < 1500 grams, inservices were provided to neonatal staff. The in-service program was discussed with the clinical unit manager as these inservices were conducted during working hours. As a matter of course, nurses were required to attend all inservices and a log was kept of all participants. Flyers were posted to remind nurses of dates and times of inservices. The inservices focused on various aspects of CPG including: (a) theoretical basis; (b) research literature which supports the proposed CPG; (c) consensus decision making -- values, beliefs, and attitudes; (d) unit policy regarding CPG (if any); and (e) the CPG. The nurses were able to access the supporting evidence and recommendations for further scrutiny. Concise recommendations and a synopsis of supporting evidence are important features of the presentation of CPG and may enhance the use of CPG in practice (Hayward et al., 1996). The supporting evidence, recommendations, and values, beliefs, and attitudes inherent in consensus decision making were made explicit in the inservices provided as they influence acceptance of guidelines (Lewis, 1995). A recorder made notes of all feedback. The feedback was appraised by the NGMRG and based on group consensus, the guidelines were finalized. Nurses were encouraged to approach any member of the panel involved in guideline development, with issues related to the guidelines.
5.2.2 Rogers' theory of diffusion: conceptual framework for adoption or rejection of CPG

Rogers' (1983) theory of diffusion of innovations was used to understand the process of adoption (or rejection) of CPG. This discourse identifies strategies used to promote nurses' adoption of CPG. In identifying these strategies, consideration was given to planning and policy development. The theory of diffusion of innovations was critically appraised and recommendations were made regarding theoretical development in studying the impact of CPG on nurses and future research in this area.

Rogers' theory of diffusion of innovations defines innovation as ideas, knowledge, object or practices which are perceived by an individual, a group, or an organization as being new. An innovation provides new alternatives or new means for solving problems. Historically, nurses have attempted to standardize approaches to patient care. In the past nurses have used hospital policy and procedure manuals, standard care plans, and algorithms. Today, nurses rely on CPG to standardize nursing care (Dracup, 1996). CPG "provide an important resource for carrying out nursing responsibilities" (Clarke, 1996, p. 13). CPG, therefore, can be viewed as innovations for nurses.

5.2.2.1 stages in the innovation-decision process

Rogers identifies 5 stages (see Figure 3) through which a potential adopter, in this case the nurse, passes. These stages epitomize the innovation-decision process which is an information-seeking and information-processing activity. The first stage, knowledge, takes place when the potential adopter is exposed to the existence of an innovation and
Figure 3. Five stages in the innovation-decision process.
develops some understanding of how it functions. The potential adopter seeks information about what the innovation is, and how and why it works. Such information is effectively transmitted by mass-media channels. The second stage, persuasion, transpires when attitudes (favorable or unfavorable) are formed about the innovation. The third stage, decision, involves the acceptance or rejection of the innovation. The fourth stage, implementation, occurs when the potential adopter uses an innovation. The final stage, confirmation, involves seeking reinforcement of a decision that has already been made by the potential adopter. If the individual encounters conflicting information or messages then the previous decision may be altered, that is, discontinuance will occur. An important dimension in the process is time, and the five steps usually occur in a time-ordered sequence (Rogers, 1983).

Based on the above discussion of Rogers' innovation-decision process, one can surmise that nursing inservices may be an effective communication message strategy. Nursing inservices on CPG for feeding premature infants < 1500 grams exposed nurses to the existence of an innovation. This strategy allowed nurses to develop some understanding of CPG, how they work, and the complex nature of feeding decisions in premature infants < 1500 grams. Exposing nurses to an innovation (CPG) created a need or state of dissatisfaction or frustration which created motivation for the adoption of the CPG (Rogers, 1983). Nurses who were aware of an innovation were more likely to be in the persuasion or implementation stages described by Rogers (Coyle & Sokop, 1990; Kirchhoff, 1982). It is important, however, to remember that such strategies should not
be expected to directly persuade nurses to adopt the proposed CPG.

5.2.2.2 perceived attributes of innovations

The aim of the innovation-decision process is to decrease uncertainty about the innovation. Attributes of the innovation itself may create uncertainty, therefore, increase or decrease the likelihood that the potential adopter will adopt the innovation. The individual's perception of these attributes determines the rate of adoption of innovation (Rogers, 1983). Rogers identifies five attributes of innovations. First, relative advantage refers to the degree to which an innovation is perceived to surpass the current practice it is to replace. Second, compatibility refers to the degree to which an innovation is felt to be similar to previous experience, beliefs and values, and to the needs of potential adopters. Third, complexity refers to a potential adopter's perception of the degree to which an innovation is relatively difficult to understand and use. Fourth, trialability refers to the degree to which a potential adopter may experiment with, on a limited basis, an innovation. Last, observability refers to the degree to which others are able to visualize the results of an innovation.

Nurses in the unit were disconcerted because of the great degree of variability in feeding orders among and within physicians (neonatologist, fellows, and residents) and CNS/NPs. CPG attempt to "refine decision making and to narrow practice variation to a degree unlikely to be achieved 'naturally' by the target audience(s)." (Lewis, 1995, p. 1074). The relative advantage of the proposed CPG is that they will decrease variability in practice. In addition, use of CPG will give nurses more autonomy in decisions related to
feedings (e.g., management of residuals). The relative advantage of CPG were articulated to nurses in all information-seeking activities.

Paradoxically, CPG are usually radical in relation to established practices (Lewis, 1995). CPG, therefore, may be viewed by some as lacking compatibility. The researchers involved in the development of the proposed CPG attempted to incorporate, whenever possible, certain established practices. For instance, in the MEN feeding studies and systematic review, MEN was started as early as the first day of life in some studies. However, this practice was not incorporated in the CPG because it was difficult to determine the optimum timing of MEN given in other studies MEN was started as late as eighth day of life. Additionally, commencing MEN on the first day of life would have meant further change in clinical practice which could have hindered the adoption of guidelines. Accordingly, the CPG for premature infants < 1500 grams incorporated the researchers' valuations and interpretations of the scientific research. The proposed guidelines were developed to improve feeding outcomes for premature infants < 1500 grams, hence, these outcomes would not be attained if the proposed guidelines were not adopted by nurses (Redman, 1996). “The development of guidelines for which there is no receptive practitioner or patient audience will be of no long-term benefit, regardless of one’s position in the health care system” (Battista & Hodge, 1995, p. 1236).

The CPG for feeding premature infants < 1500 grams were stratified, based on birth weight, into 3 weight categories, namely, < 750 grams, 750 grams to < 1000 grams, and 1000 grams to < 1500 grams. To ensure ease of use, the set-up of the CPG was identical
in each weight group. Consistent terminology was used, for example, timing, route, and type of feed. As well, the language was simple and easy to understand. The feeding guideline for infants in each weight range appeared on a separate sheet of paper. Consequently, each infant had only one guideline allocated at the time of admission and followed during the course of their stay in the unit. Upon admission of the infant, the nurses made a decision with regard to the appropriate feeding guideline. Having guidelines for each weight group on a separate sheet eliminated the burden on nurses in making a decision at each feed as to which was the most appropriate guideline. As well, as the infant gained weight there was no confusion as to which was the appropriate guideline.

Some aspects of the proposed guidelines did not differ dramatically from current practice in the unit. Over the 3 years prior to implementation of guidelines, clinicians had been starting feeds earlier in the infants’ hospital course. Research findings indicate that feeds should be initiated even sooner than the current practice. Hence, components of the CPG have been trialed in practice to some extent. When the CPG were introduced, component(s) which were currently practiced, but practiced inconsistently, were pointed out.

The advantage of the innovation over the previous practice is usually unknown. As a result, the innovation creates uncertainty. To cope with the uncertainty the individual, group, or organization, seek new information about the innovation (Rogers, 1983; Romano, 1990). During the presentation, time was devoted to discussing the efficacy and
safety of the CPG. Consequently, nurses were able to develop a perception of the observability of the innovation, that is, the degree to which others are able to visualize the result of the innovation (Rogers, 1983, 1995). For example, with the introduction of CPG, nurses would observe that it took less time for infants to reach full feeds.

Innovations that are perceived to posses attributes of relative advantage, compatibility, complexity, trialability, and observability, are usually adopted rapidly (Rogers, 1983, 1995). A meta-analysis of 23 studies examining practitioners' compliance with practice guidelines revealed that 47% of the variation in compliance rates were the result of perceived attributes of innovations. Guidelines had greater compliance if they were less complex and relatively more trialable (Grilli & Lomas, 1994). Rogers (1995) states that other factors also affect compliance rates and further research is needed in this area.

5.2.2.3 diffusion: components and as a social process

During persuasion and decision stages of the innovation-decision process, the potential adopter seeks innovation-evaluation information such as the attributes of innovation. Innovation-evaluation information facilitates the potential adopter's understanding of the advantages and disadvantages of the innovation to his or her situation. Interpersonal networks with colleagues are especially important as they provide information and subjective evaluations of innovations (Rogers, 1995). As uncertainty of an innovation increases, so does the degree of influence of interpersonal networks with colleagues (Mittman et al., 1992). The rate of adoption of an innovation is dependent on
the interpersonal networks because it forms a significant mass of new adopters (Rogers, 1995).

"Diffusion is the process by which an innovation is communicated through certain channels over time among the members of a social system" (Rogers, 1983, p. 34). The first component of diffusion, innovation, has already been discussed. The second component of diffusion, communication channels, refers to the means by which information is passed from one individual to another. Interpersonal channels or face-to-face exchange between individuals are most effective in persuading an individual to adopt an innovation. The scientific evaluation of the innovation is secondary. Communication between individuals is most effective when the two individuals are similar in certain attributes such as education, beliefs, and so forth (Rogers, 1983, 1995).

The third component, time, is an important element in the innovation-decision process that involves first knowledge of innovation to adoption or rejection of an innovation. Time is also an important element in the innovativeness of an individual. Innovativeness refers to how early or late an innovation is adopted by an individual. Adopters have been categorized based on their innovativeness. Innovators, usually few in number, are the first individuals to adopt an innovation. Innovator characteristics are as follows: (a) ability to cope with greater degree of uncertainty of innovation; (b) active information seekers; (c) external interpersonal networks as a result of travel and reading; (d) high exposure to mass media; and (e) ability to depend on objective rather than subjective evaluations of the innovation. Innovators, however, have limited ability to
influence other individual's behavior as they are not integrated with their peers in local networks (Rogers 1983, 1995).

Early adopters or opinion leaders, on the other hand, are well respected, similar to their peers, and well regarded for making reasonable decisions in adopting an innovation. Early adopters are viewed as being credible, that is, they are perceived as competent and trustworthy. As a result, once early adopters have adopted an innovation, the rate of adoption of an innovation takes off because the early adopters serve as role models for many other members of the social system. Early adopters convey the subjective evaluation of the innovation to near-peers (Rogers, 1983) and reflect the established behavior patterns, or norms, of a social system. Social system, the fourth component of diffusion, is "defined as a set of interrelated units that are engaged in joint problem solving to accomplish a common goal" (Rogers, 1983, p. 24). Individuals, informal groups, organizations, and/or subsystems comprise members of a social system. The process through which early adopters bring about change in norm which motivates change is unknown (Rogers, 1995).

Later adopters are the skeptics of the social system. Certain conditions must prevail before later adopters will adopt the innovation. First, most other individuals in the social system must have adopted the innovation. Second, the norms of the social system must favor the innovation. Lastly, there has to be some degree of peer pressure to motivate later adopters (Rogers, 1983).

No relationship has been found among those who attend continuing education
sessions, professional reading (i.e., nursing) (Brett, 1987; Coyle & Sokop, 1990; Kirchhoff, 1982; Michel & Sneed, 1995), or professional memberships (Brett, 1987; Coyle & Sokop, 1990; Kirchhoff, 1982) and adoption of innovation. These variables do not relate to exposure to research results, hence, do not correlate with awareness of innovation (Kirchhoff, 1982). Communication channels such as reading specific journals (i.e. American Journal of Nursing or Hear & Lung), number of journals read, and hours per week spent reading correlated with level of awareness (Coyle & Sokop, 1990; Kirchhoff, 1982). Additionally, there was a relationship between these variables and adoption of innovation (Brett, 1987). Kirchhoff (1982), however, found that these variables did not significantly affect persuasion and adoption of innovation. She concluded that other variables, such as interpersonal channels, were thought to be necessary for persuasion and adoption.

The medical drug-diffusion study, that examined the spread of tetracycline among physicians, clearly demonstrates the social nature of diffusion. Physicians learned about tetracycline by word of mouth (Rogers, 1995). Lewis (1995) states that clinicians respond more readily to opinions of respected colleagues and local leaders. Even when the scientific community cautions individuals about the application of certain research findings to practice, these findings disseminate among practicing nurses (Brett, 1987). One should, therefore, think of nurses as "an interconnected network of individuals" (Rogers, 1995, p. 327) which offers a lever for changing behavior (Rogers, 1995). The ten CNS/NPs may play a critical role in persuasion and adoption of CPG as a significant relationship has been
found between the adoption of research findings and the number of clinical specialists (Brett, 1987).

No relationship has been found between existence of policies and adoption of innovation (Brett, 1987, 1989). Perception of the existence of policy, however, accounted for the variance in adoption of innovation (Brett, 1987; Coyle & Sokop, 1990; Michel & Sneed, 1995). It is not clear whether perception of policy leads to behavior or vice versa. Given the degree of relationship between policy perception and variance in adoption of innovation, further research is needed in this area (Brett, 1987).

Studies examining the contribution of other social system variables, such as organization structure, particularly the size of institution; to differences in the diffusion rate of innovations, show conflicting findings (Brett, 1987, 1989; Kirchhoff, 1982; Romano, 1990). The contribution of organization complexity (formalized versus centralized) (Brett, 1987) and transformation (restructuring, reengineering and/or unionization) to differences in the diffusion rate of innovations have not been studied in nursing. Given the current state of flux in institutions, it is important that future studies measure individual and other social system variables such as informal groups, organizations, and/or subsystems.

Within an organizational context, an individual's motivation to innovate is directly related to availability of resources, that is, the more resources available the higher the motivation. Motivation, however, has little impact on adoption of innovation if resources are unavailable and training is absent. An individual's motivation to innovate is inversely
related to obstacles. Three types of barriers have been identified: historical (autonomy of practitioner), structural (practice environment) (Lewis, 1995; Grimshaw & Hutchinson, 1995; Mittman et al., 1992), and psychological (inability to relate data to circumstances) (Lewis, 1995).

5.2.3 Implementation of CPG

Implementation strategies "comprise processes which aim to improve targeted group's compliance with the recommendations, in other words, to turn changes in knowledge and attitudes into changes in practice" (Grimshaw & Hutchinson, 1995, p. 913). In addition, implementation aims to overcome the barriers to the use of the knowledge (Lomas, 1993). The extent to which CPG are incorporated in practice will determine how useful they are. Consequently, the implementation process is thought to be the most difficult step in the process (Clarke, 1996).

Studies report higher use of nursing research among nurses with a master's degree than nurses with a baccalaureate degree (Bostrom & Suter, 1993; Michel & Sneed, 1995; Stetler & DiMaggio, 1991). Since the CNS/NPs are master's prepared, they were more likely to implement the CPG in practice. Dissemination strategies were, therefore, directed first to the CNS/NP group. The CNS/NPs' clinical education sessions were used by the researchers to disseminate the CPG.

To ensure that guidelines are incorporated into practice it is imperative that the CPG be endorsed by respected colleagues (Hayward et al., 1996; Niesen & Quirk, 1997). The CNS/NPs were a valuable resource in assisting nurses to use the CPG. The ten CNS/NPs
in the unit are an important group of individuals as they embody the characteristics of the innovator. More importantly, they are regarded highly by the nurses in the unit. The implementation of CPG by the CNS/NPs and their participation in dissemination and diffusion of CPG, would highlight their expectations of the staff nurses (Niesen & Quirk, 1997). Additionally, the CNS/NPs would know what strategies would facilitate the acceptance of the CPG and reduce barriers to implementation of CPG (Niesen & Quirk, 1997). A supportive practice environment will decrease the structural barrier to CPG implementation.

Journal club, held once a month, offers nurses the opportunity to read and critically appraise nursing research. The journal club was used to review research findings on feeding premature infants < 1500 grams. Exposure to research literature enabled nurses to examine certain attributes of the CPG, for example, relative advantage. In doing so, nurses were able to relate data to their individual practice, thereby, decreasing the psychological barrier to CPG implementation.

Opinion leaders will indirectly encourage near-peer communication about the CPG (Rogers, 1995). The proposed strategy relies on influential individuals to transmit norms and/or to model appropriate behaviors as a means of changing practice patterns (Mittman et al., 1992). Much effort was concentrated on promoting the CPG to opinion leaders. Because the nurses work in teams, opinion leaders were identified in each of nine teams. These opinion leaders were resource nurses, who are senior nurses who rotate through the role every 3 months, and individuals who expressed an interest in and provided feedback
on the CPG. The nurse transport team members were also identified as opinion leaders. One of the investigators attended a resource nurses’ meeting and transport team meeting to present the CPG.

Promotional activities directed at opinion leaders enabled the researchers to substitute new norms and beliefs for those currently underlying nurses’ behaviors. These activities enabled the researcher(s) to provide subtle, implicit or explicit suggestions to the opinion leaders regarding the acceptability of the CPG (Mittman et al., 1992).

Promotional activities included academic detailing (one-on-one interactions), peer discussions, and consultation. These activities took place early in the implementation process because their impact was likely to be strongest at this time (Kaluzny, Konrad, & McLaughlin, 1995).

Ideally, CPG have been developed to influence those individuals at risk of practicing as outliers because their actions would result in either poor quality or unnecessary utilization. In reality, the influence of CPG may be greatest among those who need them least. In most instances the high-need groups are active or passive resisters who claim "No one's going to tell me how to practice ..." (Lewis, 1995, p. 1074). Opinion leaders were encouraged to provide clinical preceptorship to these later adopters. Clinical preceptorship involved assisting nurses to use CPG by reviewing the CPG for the specific weight category of the patient for whom the nurse was caring. Clinical preceptorship may afford the degree of peer pressure necessary to motivate later adopters. Active diffusion of innovation will result in faster adoption of the CPG (Kirchhoff, 1982). Given that
certain conditions must prevail before later adopters will adopt the innovation (i.e., social system must favor the innovation), the proposed strategy was instituted much later in the implementation process. In instances where resistance was encountered, attempts were made to reframe or redefine the information on CPG to offer an alternate perspective to resisters. For example, the nurses were encouraged to view the CPG as a strategy to ensure that everyone (medicine and nursing) was speaking a common language, and that this collective effort would provide a more systematic approach to feeding infants. A change in perspective enabled advocates of CPG to form an alliance with resisters of CPG, thereby, facilitating the implementation of the CPG (Kaluzny et al., 1995).

Change in practice is more likely if guidelines are disseminated by specific educational interventions and implemented with reminders during the consultation (Grimshaw & Hutchinson, 1995). The researchers reminded CNS/NPs and opinion leaders, who in turn, reminded nurses of CPG for feeding premature infants < 1500 grams. Additionally, admission orders guided nurses to CPG for nutritional management. Currently, orders have to be written on all aspects of care including nutritional management.

The CPG for feeding premature infants < 1500 grams were developed locally at a time when there was great change in the organization structure. There is no literature on how organizational circumstances influence the impact of CPG on changing nurses’ behaviors. Consequently, it was difficult to postulate specific strategies. It is imperative, however, to keep abreast of organizational changes and appraise their impact on CPG
implementation. Doing so will allow the researchers to be proactive and to implement appropriate strategies to ensure that there is change in behavior and the change is sustained. The researchers kept a log book to record all significant events in the unit which, potentially, would impact on implementation of CPG.

5.2.4 Critical appraisal of theory, research and recommendations

Rogers' (1983) theory of diffusion, in particular, the innovation-decision process, applies to decisions made by a single individual. The innovation-decision process does not focus on the individual's response to sociopolitical influences, for instance, the complex nature of the present health care environment. Rogers' theory assumes that the target system, nurses, is natural and there are no driving or restraining forces within it. The innovation-decision process is linear and assumes that actions are purposive, intentional, goal directed and rational (Romano, 1990). Nurses, however, may act irrationally out of fear and anxiety about change, competition, and jealousy, and other forces (Backer, 1995). Rogers' theory assumes that nurses have a choice of adopting or rejecting change. Within the organization there was great impetus to use CPG, therefore, nurses may not have had a choice and may have been pressured into using CPG.

Although Rogers' theory of diffusion explains diffusion as a social process, research has centered on the individual and neglected to explore the effects of the organization on adoption of innovation (Romano, 1990). Additionally, research on diffusion of innovation is plagued by methodological problems. Methodological problems include: (a) poor study design (case studies); (b) lack of validated measurement techniques; (c) focus on number
of innovations adopted rather than on process; (d) measurement of dependent and independent variables varied from study to study; and (e) confusion in terms, such as adoption and diffusion (Romano, 1990). Results of the research, therefore, cannot be generalized.

A major limitation of the research on diffusion of innovation is its pro-innovation bias which implies that all members of a social system should adopt an innovation (Romano, 1990). The rejection or discontinuance of innovation is, therefore, ignored. CPG are rarely evaluated because of lack of money and resources (Carter et al., 1995). Studies evaluating CPGs have detected significant improvements in the process of care after the introduction of guidelines. The size of improvements in performance, however, was variable. Although CPG cost money, up to $1 million per guideline, no cost effective analysis has been done (Grimshaw & Hutchinson, 1995). The discontinuance or rejection of CPG is important to prevent diffusion of ineffective, harmful and/or costly CPG. Hence, research on diffusion of innovation should evaluate the consequences of adoption or rejection of innovation to both the individual (nurse and patient) and social system.

Future research in the area of diffusion of innovation needs to focus on diffusion of innovation as a process, for instance, the process through which early adopters bring about change in behavior. Better understanding of factors which affect compliance is also needed. As well, political approaches to decision making need to be considered (Romano, 1990). Organization theory, such as the resource dependency model, may be useful in understanding the role of the external environment (i.e., political) on individual and
hospital adoption of innovation (Romano, 1990). Social influence theory, based on social psychology, sociology, health behavior change and health services research, may be useful in understanding economic and other related influences on behavior (Mittman et al., 1992). Social influence theory "offers a potentially valuable basis for implementing practice guidelines and changing practitioner behavior" (Mittman et al., 1992, p. 415).

5.3 Setting

The setting for the research was a 33-bed NICU of the Children's Hospital at the Hamilton Health Sciences Corporation, McMaster Site. The average number of admissions per year is 800 to 1000, the majority of whom are in-born. Approximately 20% of these admissions are infants weighing < 1500 grams at birth. Two teams of clinicians, residents and CNS/NPs, provide care to the infants and families. The resident team is supervised by a neonatal fellow, and each team is accountable to an attending neonatologist. The residents rotate through the NICU every 2 months and the attending neonatologist changes every month. A total compliment of ten CNS/NPs, 2 residents, on the average 4 neonatal fellows, and 7 neonatologists work in the NICU. Each clinician writes feeding orders for the infant they are managing.

The nursing staff consists of 109 registered nurses whose experience and knowledge range from novice to expert. The nursing care delivery model which is practiced is primary care nursing. Emphasis is placed on family-centered care with an appreciation of the diversity of cultural, educational and socioeconomic backgrounds of families with infants in the NICU.
5.4 **Design: Strengths and Limitations**

A before and after matched cohort study (see Figure 4) was undertaken to test the efficacy and safety of CPG for premature infants < 1500 grams. During the before study period, August 1, 1996 to August 23, 1997, data were collected on infants enrolled in the Standard Practice group. The CPG were implemented the week of April 20\(^{th}\), 1998. Data collection for the after period of the study began in mid-August, 1998, 4 months after the implementation of the guideline, and ended on May 17, 1999. During this time period data were collected on infants enrolled in the CPG group.

A before and after study is a quasi-experimental time series design in which history may threaten internal validity (Talbot, 1995). Therefore, matched cohorts were used. Cohorts were matched on birth weight, and gestational age; to +/- 100 grams and +/- 1 week, respectively. The instruments described below were used to collect data on all infants enrolled in the study. A record was kept of unmatched cohort infants. Both matched and unmatched infants were followed for the duration of the study period. During the course of the study any significant events were recorded such as change in staffing model, introduction of clinical pathways, and so forth. Recording such events enabled the investigators to determine the possible effect(s) of outside events on the outcome (Talbot, 1995).

5.5 **Inclusion and Exclusion Criteria**

All infants admitted to the NICU during the study periods, who were < 1500 grams and had no major congenital anomalies, particularly of the gastrointestinal tract, were
Figure 4. Flow diagram of study design

Abbreviations: clinical practice guidelines (CPG)
enrolled in the study. Infants were excluded if they had an Apgar score \( \leq 3 \) at 5 minutes of age, they were IUGR, or if size-at-birth standards were not available, due to extreme prematurity (i.e., < 24 weeks gestational age), to determine if they were appropriate for gestational age. Battaglia and Lubchenco’s (1967) classification by weight and gestational age was used to identify infants who were IUGR (see Appendix D) as this classification included infants 24 weeks gestation. Infants were also excluded if they developed NEC, gastrointestinal complications such as volvulus, or care was withdrawn prior to initiation of feeds. Twin infants were considered as individual babies. The instruments described below were used to collect data on all infants enrolled during the study period.

5.6 Data Collection

Two record forms were used by the investigators to follow infants enrolled in the study. The first record form included maternal history and delivery, clinical status of the infant, and maternal medications (see Appendix E). The data were abstracted from the infant’s hospital chart and were used to assess comparability between infants in the Standard Practice group and CPG group. The second record form included information on the variables related to feeding (see Appendix F).

If a mother received 12 mg of dexamethasone or betamethasone, twice a day, for 48 hours, then this was regarded as a full course of treatment. Days to full feeds represented the number of days from the start of enteral feeds to the time the infants tolerated the prescribed total fluid intake enterally. Feeding interruptions related to feeding intolerance was defined as having \( \geq 3 \) feeds held, consecutive or non-consecutive, in a 24 hour period.
Days on TPN included the number of days from birth that the infant was receiving aminosyn and fat (lipids either 10% or 20%). Sepsis was defined as having a positive blood or cerebrospinal fluid culture. NEC was defined as Stage IIA and above based on the modified Bell Staging criteria as outlined in Appendix C.

Data collection continued until 48 hours after the infant had reached full feeds or was discharged from the hospital, whichever came first. Attempts were not made to follow the infant at the referral hospital as it would have been too time consuming and costly to inservice other centres on the feeding practice guidelines for VLBW infants. The sample size calculation took into account the attrition rate of infants transferred out of hospital prior to reaching full feeds. The attrition rate will be reported and attempts will be made to explain how the rates may have affected the study results.

Two investigators, a graduate student, and a research assistant were involved in data collection. Since multiple data collectors were involved, inter-rater reliability was assessed. Data collectors used the same instruments to collected data independently on 10% of the sample. A reliability assessment score of 70% agreement or higher was considered as acceptable for group level comparisons (Talbot, 1995). The reliability assessment score ranged from 76% to 85%. Disagreements were most common in the variable, “days to full feeds”, however, the difference between observers was usually +/- 1 day.

5.7 Sample Size Justification

Sample size calculation was based on data collected for a pilot study (see Appendix
A) prior to the introduction of the CPG. Data on days to full feeds was used to calculate the sample size. A difference of 4 days was felt to constitute a clinically significant difference. Based on a 2-tailed unpaired test, alpha level of 0.05 and power of 0.8, the sample size was estimated at 100 per group. An attrition rate, of infants transferred out of hospital prior to reaching full feeds, of approximately 20% was also considered in the calculation.

5.8 Statistical Analysis

Data were analyzed using the SPSS for Windows statistical program. All statistical analyses were done based on intention-to-treat, unless stated otherwise, and were two-tailed. Descriptive statistics were used to compare infants in the two groups, Standard Practice versus CPG. Chi-square tests, like the Fisher’s exact test or Pearson chi-square, were used for comparison of categorical variables, for instance, birth number. The normality of distribution of continuous variables, such oxygen requirement, was assessed using the Kolmogorov-Smirnov test. Graphical plots, such as the normal probability and detrended normal probability plots, were also scrutinized to assess departures from normality. Since continuous variables were asymmetrically distributed in unimodal manner, that is, not normally distributed, intergroup comparisons were made using the Mann-Whitney U test. Additionally, all continuous variables are reported as median and ranges.

Because of the multiple comparisons, a p value of < 0.008 was considered to be statistically significant for maternal and delivery characteristics to ensure that the
differences, if any, was not due to chance. Setting a more stringent alpha level by applying the Bonferroni correction accounts for the increased probability of making a Type 1 error on any one comparison. The Bonferroni correction, therefore, compensates for the total number of comparisons being made by dividing 0.05 by the number of comparisons (Norman & Streiner, 1994). Based on the Bonferroni correction, for infant characteristics, a p value of < 0.006 was considered statistically significant.

The primary outcome variable was days to full feeds, a primary end point of feed tolerance. Secondary endpoints of feed tolerance, namely number of feeding interruptions related to feeding intolerance and days on TPN, were also measured. Other outcomes evaluated were days to regain birth weight, days to discharge from hospital, incidence of sepsis and NEC, and use of prokinetic agents such as erythromycin and cisapride. Logarithmic transformation of the data yielded a normal distribution, hence, paired t-tests were utilized to determine statistical inference for outcome variables that were continuous, for instance, days to full feeds. Since infants were matched for birth weight and gestational age, categorical outcomes, including incidence of sepsis, NEC, and use of prokinetic agents, such as erythromycin, were analyzed using the McNemar chi-squared analysis. Nonparametric statistics make no assumptions about the nature of the distribution of data, hence, it was not necessary to transform categorical data for analyses. A p value of < 0.05 was regarded as statistically significant for the paired t-test analysis for the primary outcome of days to full feeds. For secondary outcomes, a p value of < 0.007 was considered significant.
Because maternal antenatal celestone use, indomethacin, given for PDA closure, and lack of compliance with CPG may have impacted on the outcomes of this study, post-hoc analyses involved examining separately, subsets of patients using univariate analysis (because of limited number of subjects in each group). The Mann-Whitney U test was applied to data that were not normally distributed. Multiple stepwise linear regression analysis was undertaken to determine the contribution of the following cofactors: gestational age, mode of delivery, maternal antenatal celestone, prolonged rupture of membranes, ventilation requirement, indomethacin, erythromycin, cisapride, age when feeds were commenced, study period, and number of days feeds were interrupted because of feeding intolerance.

5.9 Plan for Protection of Subject’s Rights

5.9.1 Informed consent/risks and benefits

The researchers submitted the study to the McMaster University Faculty of Health Sciences and Affiliated Institution, Hamilton Health Sciences Corporation, Committee For Ethics For Research. The Research Ethics Board found the study to be acceptable on both ethical and scientific grounds (Appendix G).

The CPG reflect the current research in the area of nutritional management of premature infants. Only those practices which have been shown to benefit infants or where benefit has not been proven but are part of standard practice, were incorporated in the guidelines. As a result, the infants were at no additional risk following implementation of these guidelines. Since the research involved no more than minimal risk to the infants,
informed consent was not obtained.

All medical and nursing staff were educated on the feeding practice guidelines for premature infants < 1500 grams. The study was used to monitor and improve clinical practice related to feeding VLBW infants. Hence, waiving informed consent would not adversely affect the welfare of the infants. Periodically, a integrated review of the literature was undertaken to update the CPG to ensure its validity. If deemed necessary, additional pertinent information could have been provided to parents after enrollment of the infants. The need for this did not arise.

5.9.2 Confidentiality

Case numbers were used to identify patients enrolled in the study. Only the researchers had access to the recording forms used to collect data, and to the analysis forms. The materials related to the study were kept in a locked drawer in the principal investigator's office. Any publications resulting from this study will not identify patients by name.

5.9.3 Dissemination of results

Study findings will be dispersed through peer review journals to pediatric and neonatal medical and nursing colleagues. Data will be presented at local and international conferences and may include: The National Association of Neonatal Nursing Conference, Society For Pediatric Research, and perinatal conferences and workshops.
Chapter 6

Results

6.1 Introduction

The first section of this chapter will center on demographic and clinical characteristics and will address subject matters such as the study environment and eligible population. Descriptive statistics of study participants will be presented in section two. The third section will disclose the research findings as they relate to the research question. A summary of findings will be presented at the closing of this chapter.

6.2 Demographic and Clinical Characteristics

6.2.1 Study environment

Three months after the implementation of the feeding practice guidelines, staff were informally surveyed to establish the level of comfort with using the guidelines. It was apparent from the responses of individuals and periodic audits of charts that the CPG were not being adhered to completely. Two issues were identified. First, feeds were being increased even when infants were having residuals of > 50% or 1 cc, whichever was greater. The guidelines stipulated how much and how often the feeds should be increased but did not stipulate when feeds should not be increased. Second, it appeared that nurses had changed from being very conservative with how they handled residuals to being very liberal. For example, if a baby was feeding 2 cc every 2 hours and having a residual of 2
cc, according to the guidelines, the feeding should be held and the abdomen assessed. If the clinical exam was abnormal, then either the physician or CNS/NP should be contacted. If the exam was normal, then the infant should be reassessed prior to the next feeding. Instead, the 2 cc residual was being refed, sometimes with the additional 2 cc feed, making the intake for that feed 4 cc, and the physician or CNS/NP was not asked to assess the infant even when the clinical exam revealed abdominal distention with a “loopy” looking abdomen. All staff were e-mailed with regard to the two issues identified. Additionally, two investigators approached staff nurses, on a one-to-one basis, to provide clarification.

In view of the issues identified, it was decided that the staff nurses should be given more time to become accustomed to the CPG; additional educational sessions were deemed unlikely to offer benefit. Data collection, therefore, did not begin until August 23, 1998, 4 months after the implementation of the guidelines. In the after period, the only significant changes in practice which might impact feeding management and the outcomes of this study, were the use of cisapride and the use of a new nursing documentation sheet.

Cisapride is a gastrointestinal prokinetic agent for managing feeding intolerance secondary to decreased gastrointestinal motility. Janssen-Ortho Inc. circulated important safety information in a letter, dated July 22, 1997, to all health care professionals regarding the use of cisapride in premature infants. The use of cisapride was contraindicated in premature infants born at < 36 weeks gestation, from birth through 3 months after the delivery date (M. Marrin, personal communication, July 22, 1997). Concerns regarding drug interactions leading to elevated levels of cisapride and
prolongation of cardiac conduction intervals, particularly QTc, were cited as reasons for the contraindication. In accordance with Janssen-Ortho Inc.'s safety recommendations, the use of cisapride was discontinued in this population of infants on September 10, 1997. As a result, there was only 1 infant in the CPG group who received cisapride for feeding intolerance compared to 16 infants in the Standard Practice group. Since the difference in use of cisapride was reflective of a change in unit policy, its use in clinical practice will be examined as a confounding variable, in Chapter 7, which may possibly influence the other outcomes in this study.

Nurses used two flow sheets, one to document vital signs, oxygenation, and miscellaneous items. The other flow sheet was used for feeding orders, intravenous fluids, and urine, stool, and gastric output. These two flow sheets were consolidated into one "neonatal unit daily flow sheet". The new flow sheet was introduced in early October, 1997. The impact of this change in documentation remains unclear. Anecdotally, it was somewhat easier to extract the data; however, similar gaps or errors were evident in documentation by the nurses. For example, errors in calculation of cumulative totals for intravenous fluids, and the absence of double signatures for checking and giving expressed breast milk continued to be an issue.

6.2.2 Eligible population

Data for the before-study period were collected between August 1, 1996 and August 23, 1997. The month of January 1997, however, was inadvertently missed. During the data collection period, 183 infants who were < 1500 grams were admitted to the NICU.
All infants were screened for eligibility and 126 (69%) initially qualified for the before-study period.

Figure 5 depicts a flowchart of all infants admitted during the before-study period, that is, infants included in the Standard Practice group, and delineates reasons for exclusion and loss to the study after meeting the initial inclusion criteria. In the initial screen for inclusion and exclusion, infants were excluded for the following reasons: IUGR (16%), inability to establish the presence of IUGR (no size-at-birth standards exist for infants ≤ 23 weeks) (1%), congenital anomalies including tracheoesophageal fistula, bowel compression secondary to bands, and Down syndrome (2%), no Apgar score documented or Apgar score ≤ 3 at 5 minutes (1%), maternal history of cocaine use in which twin infants delivered to this mother tested positive for cocaine (1%), late transfer (day 15 of life) to the NICU (0.5%), and early neonatal death (10%).

Of the 126 infants who met the inclusion criteria, 10 (8%) were lost to the study for the following reasons: the chart of 1 infant could not be retrieved (0.8%), early transfer (at day 5) of an out of region infant born at 24 weeks gestation (0.8%), protracted hypoglycemia (0.8%), perforated NEC (1 infant was never fed and the other received only 1 feeding) (2%), and late neonatal death (4%). Of the five late neonatal deaths, three infants were never fed. Of the two who received feedings, one infant received only three feeds, and one infant was fed for five days after which time feeds were discontinued because of large volume residuals and abdominal distention. The first infant had a cardiorespiratory arrest on day 12 of life and could not be resuscitated. The second infant
Figure 5. Flow chart of infants admitted to the NICU and included in the Standard Practice group.

Abbreviations: intrauterine growth restriction (IUGR); necrotizing enterocolitis (NEC); neonatal intensive care unit (NICU)
had congenital herpes simplex encephalitis with cutaneous lesions and care was withdrawn on day 15 of life after a cardiorespiratory arrest.

Because of the unusually large number of survivors who were 24 to 25 weeks gestational age, data were collected on more than 100 infants (n=116) to ensure that appropriate matches could be found in the CPG group. Data on the first 100 babies who could be matched on birth weight (+/- 100 grams), and gestational age (+/- 1 week) were analyzed for this study.

Data for the after-study period were collected between August 23, 1998 and May 17, 1999. During this time period there were 159 infants admitted to the NICU, who could be potentially enrolled in the CPG group (see Figure 6). In the initial screen for inclusion and exclusion, infants were excluded for the following reasons: IUGR (11%), inability to establish the presence of IUGR (no size-at-birth standards exist for infants ≤ 23 weeks) (0.6%), congenital anomalies including tracheoesophageal fistula, imperforate anus, and Down syndrome (2%), no Apgar score documented or Apgar score ≤ 3 at 5 minutes (3%), maternal history of thalassemia and severe anemia requiring multiple transfusions (1%) [this mother delivered twins, one of whom had a sacral skin defect which was suspected to be spina bifida], late transfer (day 4 of life) to the NICU (0.6%), and early neonatal death (8%).

Of the 115 infants who met the eligibility criteria, 8 (7%) were lost to the study for the following reasons: early transfer of an out of region infant (0.9%), perforated NEC (3%), volvulus (0.9%), and late neonatal deaths (3%). There were 107 infants who were
Figure 6. Flow chart of infants admitted to the NICU and included in the CPG group.

Abbreviations: clinical practice guidelines (CPG); intrauterine growth restriction (IUGR); necrotizing enterocolitis (NEC); neonatal intensive care unit (NICU)
available, however, seven infants could not be matched and were therefore excluded from
the analysis.

Of the three infants who developed perforated NEC, two infants were never fed. The third infant received only 3 feeds beginning on day 6 of life. Feeds were initiated late
because of persistent PDA requiring surgical ligation on day 10 of life. On day 8 of life
this infant was found to have perforated NEC and died on day 11 of life from internal
hemorrhage secondary to a liver laceration, post peritoneal drain insertion.

Of the 3 late neonatal deaths (not including the infant described above), 2 infants
were never fed. The third infant received feeds starting on day 5 of life. Feeds were
discontinued after 20 hours because of a PDA. This infant died on day 15 of life from
intraventricular hemorrhage and Escherichia coli septicemia.

6.3 Descriptive Statistics of Study Participants

Comparability between infants in the two groups, Standard Practice and CPG, was
assessed by examining maternal, mode of delivery and infant characteristics as outlined in
Table 11 and Table 12, respectively. There were a significantly higher number of infants
\((p = 0.003)\) delivered by cesarean section in the CPG group. Not all mothers received
antenatal steroids. Of those who did receive antenatal steroids, it was difficult to decipher
from the charting if mothers received partial or full courses of antenatal steroids.

Hence, the data were grouped together and no statistically significant differences were
found between infants in the two groups \((p = 0.02)\). There were no statistically significant
differences in the baseline infant characteristics between matched cohorts (see Table 12).
Table 11. Comparison of Maternal and Mode of Delivery Characteristics in the Study Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SP Group</th>
<th>CPG Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=100</td>
<td>N=100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>Birth number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>singleton</td>
<td>67</td>
<td>71</td>
<td>0.16</td>
</tr>
<tr>
<td>twin</td>
<td>30</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>triplet</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>quadruplet</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>36</td>
<td>58</td>
<td>0.003(^\uparrow)</td>
</tr>
<tr>
<td>ROM &gt; 24 hours PTD</td>
<td>28</td>
<td>16</td>
<td>0.04(^\ast)</td>
</tr>
<tr>
<td>Eclampsia/preeclampsia</td>
<td>10</td>
<td>17</td>
<td>0.21(^\ast)</td>
</tr>
<tr>
<td>Maternal steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>partial/full</td>
<td>85</td>
<td>74</td>
<td>0.02(^\ast)</td>
</tr>
<tr>
<td>multiple course</td>
<td>27</td>
<td>20</td>
<td>0.38(^\ast)</td>
</tr>
<tr>
<td>Transferred after birth</td>
<td>9</td>
<td>14</td>
<td>0.38(^\ast)</td>
</tr>
</tbody>
</table>

\(^\ast\) Because sample size = 100, the % and n are the same number

\(\sim\) Pearson chi-square

\(^\uparrow\) Fisher’s exact test

Abbreviations: Standard Practice (SP); Clinical Practice Guidelines (CPG); rupture of membranes (ROM); prior to delivery (PTD)
Table 12. Comparison of Infant Characteristics in the Study Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SP Group</th>
<th>CPG Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)*</td>
<td>n(%)*</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>48</td>
<td>40</td>
<td>0.32</td>
</tr>
<tr>
<td>male</td>
<td>52</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>25</td>
<td>42</td>
<td>0.02</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>22</td>
<td>26</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Md</th>
<th>Mn</th>
<th>Mx</th>
<th>Md</th>
<th>Mn</th>
<th>Mx</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen requirement (days)</td>
<td>6</td>
<td>0</td>
<td>106</td>
<td>5</td>
<td>0</td>
<td>260</td>
<td>0.6</td>
</tr>
<tr>
<td>Ventilation requirement (days)</td>
<td>4</td>
<td>0</td>
<td>54</td>
<td>6</td>
<td>0</td>
<td>122</td>
<td>0.1</td>
</tr>
<tr>
<td>Days on NP CPAP</td>
<td>4</td>
<td>0</td>
<td>32</td>
<td>2</td>
<td>0</td>
<td>38</td>
<td>0.1</td>
</tr>
<tr>
<td>Days UAC instituted</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>Days UVC instituted</td>
<td>4</td>
<td>0</td>
<td>17</td>
<td>4</td>
<td>0</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Because sample size = 100, the % and n are the same number

Abbreviations: standard practice (SP); clinical practice guidelines (CPG); Median (Md); Minimum (Mn); Maximum (Mx); nasal prong continuous positive airway pressure (NP CPAP); umbilical arterial catheter (UAC); umbilical venous catheter (UVC)
Therefore, any differences in study outcomes may be attributable to differences in rate of infants delivered by cesarean section between the two groups.

6.4 Research Findings As They Relate To The Research Question

In both groups, some infants had feeds initiated on days outside the 95% confidence intervals, that is, greater than 2 standard deviations around the median. In order to control the individual variation resulting from these outliers and extreme values, and to better understand the impact of the CPG on the outcomes of this study, data were re-analyzed after excluding infants represented by these outliers and extreme values in age when feeds were commenced.

6.4.1 Age when feeds were commenced

In order to ascertain if CPG were being implemented, the age when feeds were commenced was compared between the infants in the two groups (see Figure 7). In the Standard Practice group, 55 infants had feeds initiated at or before 48 hours of age compared to 40 in the CPG group. This difference was not statistically significant (p = 0.7) based on the McNemar test. The median age at which feeds were commenced in the Standard Practice group versus the CPG group was 2 and 3 days, respectively.

The boxplot of age when feeds were commenced, Figure 7, reveals that both groups had outliers, indicated by the open circle, however, there were more outliers in the Standard Practice group compared to the CPG group. Both groups also had extreme values indicated by the asterisk, however, there were four values in the CPG group compared to three in the Standard Practice group. These outliers and extreme values may
Figure 7. Boxplot of age when feeds commenced in the Standard Practice group and CPG group.

Abbreviations: clinical practice guidelines (CPG); outliers (○); extreme values (*)
represent infants who were critically ill, hence, were not deemed stable enough by the clinician to have feeds initiated early. Although these outliers and extreme values could potentially impact on the study outcomes, the infants represented herein delineate the feasibility of implementing CPG in such a diverse population of infants. A paired sample t-test showed no significant difference between groups even after excluding infants, identified as outliers and extreme values for age when feeds were commenced, from the analysis (see Table 13).

6.4.2 Time (days) to full feeds

As previously stated, days to full feeds represents the number of days from the start of enteral feeds to the time the infants tolerated the prescribed total fluid intake enterally. In certain cases, the volume of feed could not be increased to the prescribed total fluid intake as the infant had a peripheral or central venous dextrose line for the purpose of delivering medications and maintaining patency. In such instances, if the infant was tolerating the prescribed volume of enteral feed taking into account the intravenous line, then it was considered that the infant had reached full feeds. For example, if the total fluid intake ordered was 7 cc per hour and the infant had a intravenous line with dextrose infusing at 1 cc per hour, then full feeds was attained when the infant was taking 12 cc of milk every 2 hours or 6 cc per hour.

In the Standard Practice group 74 infants attained full feeds during their NICU stay compared to 68 in the CPG group. The median, minimum, and maximum are reported in Table 13. Of the 26 missing infants in the Standard Practice group, 2 developed NEC and
Table 13. Comparison of Groups on Major Study Outcomes

<table>
<thead>
<tr>
<th></th>
<th>SP Group</th>
<th>CPG Group</th>
<th>All data p value</th>
<th>Select data p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>Md</td>
<td>Mn</td>
<td>Mx</td>
</tr>
<tr>
<td>Age when feeds commenced (days)</td>
<td>100</td>
<td>2</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Time to full feeds (days)</td>
<td>74</td>
<td>15</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>Number of feeding interruptions</td>
<td>98</td>
<td>1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>related to feeding intolerance (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on TPN</td>
<td>98</td>
<td>12</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Days to regain birth weight</td>
<td>62</td>
<td>19</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>Days to discharge from hospital</td>
<td>100</td>
<td>27</td>
<td>2</td>
<td>184</td>
</tr>
</tbody>
</table>

* Because sample size = 100, n also represents %

Abbreviations: standard practice (SP); clinical practice guidelines (CPG); Median (Md); Minimum (Mn); Maximum (Mx); total parenteral nutrition (TPN);
24 infants were transferred to referral hospitals prior to reaching full feeds. Of the 32 missing infants in the CPG group, all were transferred to referral hospitals prior to reaching full feeds. A paired sample t-test showed no significant difference in days to full feeds between the two groups even when infants represented by outliers and extreme values for age when feeds were commenced were removed from the analysis.

6.4.3 Feeding interruptions related to feeding intolerance

The median, minimum, and maximum for each group are reported in Table 13. The underlying etiology of feeding intolerance included PDA, persistent bilious residuals post indomethacin treatment for PDA, gastric hemorrhage of unknown cause (reported in two infants, one in each group), suspected NEC, sepsis or immaturity.

The boxplot in Figure 8 indicates that the medians and hinges (edge of each box or the 25th and 75th percentiles) of the two groups did not differ. However, the Standard Practice group had extreme or far outside values, denoted by an asterisk, while the CPG group did not. There were two infants who contributed to these extreme values. Both infants had feeds held for 18 days because of persistent problems with residuals. Both these infant’s feeding intolerance was thought to be related to immaturity; as a result, one received erythromycin and the other cisapride.

The number of outliers in the two groups, denoted by an open circle, were the same - three in each group. In the Standard Practice group, these outliers represented infants who had feeds held for either 12 or 13 days because of bilious residuals (with or without feeds) post treatment with indomethacin for closure of PDA. Subsequently, one of these
Figure 8. Boxplot of number (in days) of feeding interruptions related to feeding intolerance in the Standard Practice group and the CPG group.

Abbreviations: clinical practice guidelines (CPG); outliers (○); extreme values (*)
infants was suspected of having NEC. The second infant developed a gastrointestinal bleed which was thought to be unrelated to the indomethacin treatment given its late presentation, and the third infant developed feeding intolerance secondary to sepsis. In the CPG group, these outliers represented three infants, one of whom had developed a PDA requiring ligation and had feeds held for nine days in total. The second infant’s feeding intolerance, for which feeds were held for 10 days, was thought to be related to immaturity. The third infant had feeds held for 11 days in total for reasons that could not be deciphered from the chart.

A paired sample t-test showed no significant difference in the number of feeding interruptions related to feeding intolerance between infants in the CPG group and infants in the Standard Practice group irrespective of whether infants were outliers or extreme values, and their data were included, and then excluded from the analysis (see Table 13).

6.4.4 Days on TPN

There were two missing cases in the Standard Practice group; these were infants who developed NEC. There were 16 infants in the Standard Practice group and 26 infants in the CPG group who were transferred while still on TPN. Attempts were not made to follow these infants to determine the total duration of time they remained on TPN. Hence, for these infants the number of days on TPN was calculated as the number of days from birth to the time of transfer that the infant was receiving TPN. There were four infants in the Standard Practice group and three in the CPG group who did not receive TPN as they were transferred early, that is, prior to the protocol used in the unit to initiate TPN. One
infant in each group was discharged on the day TPN would have been initiated. Since these infants were transferred mid-day, the data sheets, which recorded variables for the complete 24 hour period, did not capture these infants as receiving TPN. For these infants the number of days on TPN was reported as zero. The median, minimum and maximum days on TPN are reported in Table 13. A paired sample t-test showed no significant difference between groups in days on TPN since birth in both analyses, that is, with and without outliers and extreme values for age when feeds were commenced.

6.4.5 Days to regain birth weight

To examine the magnitude of change in weight gain from the implementation of CPG, the number of days it took the infant to regain birth weight was recorded. A paired sample t-test showed no significant difference in the number of days it took infants to regain birth weight in the two groups. Although it appears that the range is wider in the Standard Practice group, there is only one infant who regained birth weight at day 59 (see Table 13). Even when outliers and extreme values for age when feeds were commenced were excluded from the analysis, a paired sample t-test showed no significant difference in the number of days it took infants to regain birth weight in the two groups. Since infants were not weighed on a daily basis, the values reported in Table 13 are only crude estimates of the number of days it took infants to regain birth weight. The Standard Practice and CPG groups had 38 and 32 missing values, respectively. In the Standard Practice group, two missing values represented infants who developed NEC. The rest of the infants were transferred prior to regaining their birth weight. In the CPG group all 32
infants were transferred prior to regaining their birth weight.

6.4.6 Days to discharge from hospital

All infants, including the two infants in the Standard Practice group who developed NEC, were accounted for in the analysis (see Table 13). A paired sample t-test showed no significant difference in days to discharge between infants in the two groups (p = 0.72). If the two infants who developed NEC were excluded, there was still no significant difference (p = 0.57) between groups in days to discharge from hospital. Once again, no difference was found if infants represented by the outliers and extreme values for age when feeds were commenced were excluded from the analysis (p = 0.49).

6.4.7 Incidence of sepsis

The number of infants who developed positive blood cultures and the organism(s) identified are reported for both groups in Table 14. There was no significant difference between groups in the number of infants who developed positive blood cultures, based on the McNemar test (p = 0.6). In the Standard Practice group, 4 infants had recurrent episodes of infection. Each of these infants had one subsequent blood culture that was positive for staphylococcus coagulase negative. The number of days between episodes were 3, 5, 11, and 43. In the CPG group, only 1 infant had a recurrent episode, 4 days later, of infection which was identified as staphylococcus coagulase negative. There were no positive cerebrospinal fluid cultures in the Standard Practice group compared to one in the CPG group. The organism was identified as staphylococcus coagulase negative.
<table>
<thead>
<tr>
<th>Organism Identified</th>
<th>SP Group N=100</th>
<th>CPG Group N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus coagulate negative (including staphylococcus epidermidis)</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Candida</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus Aureus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Escherichia Coli</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of positive cultures</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Number of infants with positive blood cultures</td>
<td>22(^*)</td>
<td>23(^*)</td>
</tr>
</tbody>
</table>

* Because sample size = 100, the % and n are the same number

\(^*\) One infant’s blood culture was positive for both candida and staphylococcus coagulate negative organisms

Abbreviations: standard practice (SP); clinical practice guidelines (CPG)
6.4.8 Incidence of NEC

In the Standard Practice group, four infants developed NEC, two were suspected and two with stage II or greater. In the CPG group two infants had suspected NEC. For the purpose of determining if there was a significant difference between groups in the incidence of NEC, those infants with suspected and proven NEC were grouped together. The McNemar test showed no significant difference (p = 0.6) between groups in incidence of NEC.

6.4.9 Use of prokinetic agents

There were five infants in Standard Practice group compared to four infants in the CPG group who received erythromycin for feeding intolerance. The McNemar test showed no significant difference (p = 1.0) between groups.

6.5 Summary of Findings

There was no significant difference between infants in the Standard Practice group and infants in the CPG group in:

1. Age when feeds were commenced.
2. Time (days) to full feeds.
3. The number of feeding interruptions related to feeding intolerance.
4. Days on TPN.
5. Days to regain birth weight.
6. Days to discharge from hospital.
Chapter 7

Discussion

7.1 Introduction

The findings of this study supported the null hypothesis postulated as a result of the institution of CPG. The lack of statistically significant differences in the outcomes examined in this study may be reflective of the concurrent factors that influence the outcomes measured. For instance, changes occurring in maturation of the gastrointestinal system during the observational period may have obscured the benefits of feeding practice guidelines on infant outcomes. In addition, extrauterine and intrauterine environmental factors which can alter the developmental process of the gastrointestinal system may also have diminished any impact of the CPG on the outcomes. Extrauterine environmental factors include exposure to drugs, such as cisapride and indomethacin, while intrauterine environmental factors include use of antenatal steroids (e.g. celestone), and mode of delivery. Finally, a lack of compliance by the caregivers with the CPG may also explain why no significant differences were found in the study outcomes when comparing the two groups, CPG versus Standard Practice. In order to explore the plausibility of the various explanations offered with regard to the findings of this study, and to broaden the scope of the discussion, post-hoc analyses of data are presented in the discussion which follows.
7.2 Extrauterine Environmental Factors

The similarity in feeding intolerance between infants in the Standard Practice and CPG groups may be explained by the ontogeny of the gastrointestinal system. The median gestational age of infants enrolled in this study was 28 weeks. At this gestational age, the MMC is poorly formed and shows disorganized, random bursts of motor activity (Bisset et al., 1988). It is not until 37 to 42 weeks gestational age that the MMC produces true peristalsis (Morriss, 1991). The MMC represents one of the three consecutive phases of the interdigestive cycle. The interdigestive cycle recurs every 60 to 90 minutes throughout fasting. Feeding intolerance reflects a delay in the maturation of the neonate's motor activity in that they lack complete interdigestive cycles during fasting. Additionally, infants with feeding intolerance are not able to change their pattern of motor activity in response to feeds (Bersethe & Nordske, 1992). Berseth and Nordske have demonstrated this inability to initiate the "fed response" in manometry recordings done during the fasting state. These recordings were characterized by increased clusters of motor activity, and less quiescence. This pattern of intestinal activity was transient, however, it took 4 weeks to resolve (Bersethe & Nordske, 1992). Hence, infants may be unresponsive to changes in feeding practices because the state of immaturity of the gastrointestinal system limits the infant's response to such changes.

Administration of prokinetic agents, such as cisapride, may "normalize" motor patterns, thereby promoting tolerance to feeds (Bersethe, 1999, p. 1009). Cisapride mimics the natural progression of maturation of motor activity such that there is improved
intestinal motility leading to rapid small and large bowel transit times (Barone, Jessen, Colaizzi, & Bierman, 1994; McCallum, Prakash, Campoli-Richards, & Goa, 1988). More specifically, cisapride is thought to enhance the physiologic release of acetylcholine at the myenteric plexus of the intestine. Other actions of cisapride include accelerating gastric emptying by increasing gastric and duodenal contractility, decreasing gastric reflux into the esophagus by increasing esophageal peristaltic activity and enhancing esophageal sphincter tone (McCallum et al., 1988).

Although the role of cisapride in enhancing gastric motility is well supported (Hyman et al., 1988; Vandenplas et al., 1986; Van Peer et al., 1986), there is a paucity of literature regarding its use in the neonatal population (Premji, Wilson, Paes, & Gray, 1997). An extensive literature search identified six studies of cisapride use in neonates (Deorari, Reddy, Paus, & Bal, 1999; Enriquez, Bolisetty, Patole, Garvey, & Campbell, 1998; McClure, Kristensen, & Grauag, 1999; Melis & Janssens, 1990; Janssens, 1987; Vandenplas et al., 1986). Study designs varied and included randomized, double blind, placebo control (Deorari et al., 1999; Enriquez et al., 1998), crossover (McClure et al., 1999), and reports or case series (Melis & Janssens, 1990; Janssens, 1987; Vandenplas et al., 1986). Infants included in the studies ranged from 26 weeks to 38 weeks. Methodological flaws included inconsistent inclusion criteria among studies (e.g. one study included infants with “clinically” diagnosed gastroesophageal reflux and feeding intolerance), small sample size, use of inconsistent feeding protocols (mode of feeding and type of feeding) within and among studies, varied dose (0.1 mg/kg 8 times a day to 0.16
mg/kg 4 times a day) and duration of administration of cisapride among studies, lack of blinding of outcome assessor, and single point measurements.

Earlier studies (Enriquez et al., 1998; Melis & Janssens, 1990; Janssens, 1987; Vandenplas et al., 1986) reported beneficial outcomes in variables related to feeding tolerance such as decreased gastric residuals (Enriquez et al., 1998; Melis & Janssens, 1990), decreased vomiting (Enriquez et al., 1998; Janssens, 1987; Vandenplas et al., 1986), and increased feeding volume (Melis & Janssens, 1990; Vandenplas et al., 1986). Janssens (1987) reported increased weight gain in the group of infants who were vomiting. Vandenplas et al. (1986) reported a decrease in all gastroesophageal reflux parameters measured including pH monitoring, number and length of reflux episodes. Cisapride appears to offer clinical benefit to those infants with feeding intolerance based on these earlier studies. The greater use of cisapride in the Standard Practice group may have stimulated gastrointestinal development, thereby improving feeding tolerance.

More recent studies (Deorari et al., 1999; McClure et al., 1999), however, have failed to support the findings of these earlier studies. In fact, these studies report that cisapride use is associated with adverse outcomes, including delayed gastric emptying, delayed whole gastrointestinal transit time (McClure et al., 1999), and increased incidence of gastroesophageal reflux (Deorari et al., 1999). A more serious adverse outcome of prolonged QT interval, which can lead to ventricular arrhythmias such as torsad de pointes, has also been reported in studies involving neonates (Bedu, et al., 1997; Hill et al., 1998; Lewin, Bryant, Fenrich, & Grifka, 1996; Ward, Lemons, & Molteni, 1999). The
growing concerns about these adverse outcomes secondary to cisapride use in the premature infant population has prompted, as previously stated, the producer of cisapride to discontinue its use in this population of infants.

Although indomethacin, a drug given for closure of PDA, is presumed not to affect the development of the gastrointestinal system per se, it can potentially alter the structure and function of the gastrointestinal system. Premature infants with symptomatic PDA have reduced, absent, or retrograde mesenteric diastolic blood flow velocities (Coombs et al., 1990; Shimada et al., 1994) and these reductions are further amplified with indomethacin therapy (Coombs et al., 1990; Van Bel et al., 1990; Yanowitz et al., 1998). Localized or systemic hypoperfusion and hypoxemia can lead to interrupted oxygen supply to the bowel, resulting in ischemic mucosal injury which is a common factor in the etiology of NEC (Brown & Sweet, 1982; Bauer et al., 1984). A systematic review conducted by Fowlie (1997) found a trend towards increased incidence of NEC in infants of birth weight < 1751 grams, who received prophylactic intravenous indomethacin. The pooled estimate of risk difference was 0.015 (95% confidence interval -0.002, 0.033). This systematic review included studies in which indomethacin was given within the first 24 hours of birth to reduce the mortality and morbidity associated with PDA and intraventricular hemorrhage (IVH).

In this study, infants received indomethacin when there was clinical evidence or echocardiographic confirmation of PDA. There was no statistically significant difference in the use of indomethacin between the Standard Practice group (n = 25%) and CPG
group (n = 42%). There were, however, 22 infants in the Standard Practice group who were enrolled in a randomized controlled, double blind, trial of indomethacin prophylaxis in premature infants (TIPP). The TIPP trial was underway during the time frame that data were collected for the Standard Practice group. In this study, infants < 1000 grams at birth, who met the inclusion criteria, were randomized to receive prophylactic indomethacin or placebo within 6 hours of birth. Infants received a dose of indomethacin or placebo every 8 hours for a total of 3 doses. The number of infants who may have received prophylactic indomethacin, as opposed to placebo, would be too small (n = 11) to influence the outcome of this study. Additionally, 6 of the 22 infants enrolled in the TIPP study also received “open label” indomethacin. These infants would already be accounted for as receiving indomethacin. Hence, further limiting the impact of the TIPP study on the outcomes of this study. The present study showed no significant difference in the incidence of NEC between infants in the two groups despite a difference in enrollment in the TIPP study.

It was anticipated that the CPG would promote earlier initiation of feeds. The CPG per se were followed for the 42% of infants in the CPG who received indomethacin, as the guidelines indicate that feeds should be held during indomethacin therapy. The difference in the number of infants who received indomethacin for closure of PDA between the CPG (42%) and the Standard Practice group (25%), may explain why there was no statistically significant difference between groups in age when feeds were commenced. Post-hoc analysis of the data failed to support the above hypothesis as there was no significant
difference in age when feeds were commenced when infants in the Standard Practice
group were compared to infants in CPG groups who did not receive indomethacin (p =
0.42).

Once the decision was made to commence feeds, CPG may not have been followed,
with regard to amount and frequency of feeding, and feeding advances, for infants in the
CPG group who received indomethacin. Feeding practices as such were not monitored
during the TIPP study. Clinicians may have been more cautious with feeding during the
TIPP study period due to the uncertainty of the effects of prophylactic indomethacin and
blinding to drug assignment. Hence, for infants in the Standard Practice group, when
feeds were commenced, small volumes may have been given and feeding advances may
have been slower. Although fewer infants received indomethacin in the Standard Practice
group, the cautious feeding regimen exercised because of the TIPP study, may explain
why no differences were found between groups in variables related to feeding intolerance,
such as days to full feeds and days on TPN.

Although there was no statistically significant difference in the use of indomethacin
for closure of PDA between groups, the difference may be clinically significant. One
could postulate that ischemic changes, although not serious enough to cause NEC, may
have altered the intestinal mucosa sufficiently to preclude infants from tolerating feeds and
reaching full feeds sooner. Anecdotal evidence suggests that infants who have received
indomethacin often have problems with bilious residuals either before or after feeds are
commenced. Some degree of caution is often exercised when feeding infants who have
received indomethacin, for example, feeding advances are slower than the proposed guidelines.

After excluding infants in both groups who received indomethacin, the Mann-Whitney U test showed no significant difference in age when feeds were commenced (p = 0.42), days to full feeds (p = 0.072), number of days feeds were interrupted for feeding intolerance (p = 0.35), days on TPN (p = 0.35), days to regain birth weight (p = 0.23), and age at discharge (p = 0.4). Although there was no significant difference in days to full feeds, the value does approach statistical significance. When all data for days to full feeds were included, p = 0.35, compared to p = 0.072 when babies who received indomethacin were excluded. The median(range) for the CPG group was 10(37) compared to 15(50) for Standard Practice group. The post-hoc analysis, to some extent supports the claim that the difference in indomethacin use may be clinically significant. The larger number of infants (n = 42%) in the CPG group compared to Standard Practice group (n = 25%) may, therefore, explain the findings of this study.

7.3 Intrauterine Environmental Factors

The pituitary adrenal system (NIH Consensus Conference, 1995) and the chorionic membrane (Murphy, 1977) produce cortisol which affects differentiation of organ systems such as the lung and intestine. The levels of cortisol increase with increasing gestational age (Murphy, 1978). There is an increase in cortisol levels in both maternal and fetal circulation (Grosso, MacDonald, Thomasson, & Christian, 1980; Mukherjee & Swyer, 1972; Sybulski, 1977; Sybulski & Maughan, 1976a). Infants in this study were born at a
median gestational age of 28 weeks. One could postulate that these infants may not have had an adequate level of cortisol or enough exposure to cortisol to promote differentiation, hence, maturation of the gastrointestinal system. The biological immaturity of the gastrointestinal system may explain the similarity in study findings between infants in the two groups. Intrauterine environmental factors including mode of delivery and use of antenatal steroids, which can alter the developmental process of the gastrointestinal system, may also explain the lack of difference found in this study.

A statistically significant difference was found in rates of cesarean section delivery (p = 0.003) favoring the CPG group. Additionally, although there was no statistically significant difference (p = 0.04) in the proportions of infants delivered with prolonged rupture of membranes or > 24 hours prior to delivery, these differences may be clinically significant. There were 16 infants in the CPG group compared to 28 in the Standard Practice group who met this criterion. Stressful situations during pregnancy can stimulate the production of fetal cortisol (Procianoy & Cecin, 1985; Procianoy, Cecin, & Pinheiro, 1983; Sybulski, 1977). High cord plasma cortisol levels were reported in newborn infants whose mothers had prolonged rupture of membranes for more than 16 hours prior to delivery (Bauer, Stern, & Colle, 1974).

Use of corticosteroids in the management of mothers with threatened premature delivery is of particular interest because of its role in promoting fetal lung maturation, and decreasing the incidence of respiratory distress syndrome (RDS). RDS can be a major cause of mortality and morbidity for VLBW infants (Crowley, Chalmers, & Keirse, 1990).
Corticosteroids used in practice include dexamethasone and betamethasone (celestone). Both forms are identical in biological activity and both readily cross the placenta in their biologically active forms (NIH Consensus Conference, 1995). In this study, there was no statistically significant difference in the use of maternal antenatal celestone (p = 0.02), 85 in the Standard Practice group versus 74 in the CPG group. The difference in antenatal celestone use, however, may be clinically significant because the primary effect of corticosteroids can induce maturity of certain biological events including enzyme activity and motor function in the gastrointestinal system (Morriss, Moore, Weisbrodt, & West, 1986; Henning, 1981) by converting inactive cortisone to cortisol (Bauer et al., 1984).

Secondary effects of corticosteroid include the reduction of complications which arise as a consequence of respiratory morbidity and its treatment (Crowley et al., 1990), such as NEC. Infants in this study were born between 24 and 33 weeks gestational age; the median age being 28 weeks gestation. The median days of ventilation requirement was 4 for the Standard Practice group versus 6 for the CPG group, the range being 54 and 122 days, respectively. The difference in ventilatory needs between groups were not statistically significant. There were no statistically significant differences in the incidences of NEC and sepsis between groups.

The following discussion, will examine the effect of mode of delivery, primary and secondary effects of antenatal steroid, and potential risk of sepsis with antenatal steroid use, on the outcomes of this study. Studies of term deliveries have detected no significant difference in cord blood cortisol levels in spontaneous versus induced labor, although,
lower cortisol levels were reported with elective cesarean sections without prior labor compared to vaginal delivery (Pokoly, 1973; Sybulski & Maughan, 1976b). Studies evaluating cord serum levels of cortisol in premature newborn infants have found a similar association between vaginal delivery after spontaneous onset of labor and high cord cortisol levels (Procianoy & Cecin, 1985; Procianoy et al., 1983). In both studies, those infants whose mothers received antenatal steroid therapy were excluded from the study.

Usher, Allen, and McLean (1971) found a higher incidence of hyaline membrane disease in infants delivered by cesarean section compared to those delivered vaginally when controlling for gestational age. It has been postulated that an increased level of cortisol may play a role in preparing the fetal lung for extraterine life (Sybulski, 1977) as infants with hyaline membrane disease have been reported to have low cord cortisol levels (Kauppila, Koivisto, Pukka, & Tuimala, 1978; Murphy, 1974; Sybulski & Maughan, 1976a). Similarly, the elevated cortisol levels may play a role in preparing the fetal gastrointestinal system for extraterine life. At birth, there are profound changes in nutrition and trophic factors, such as surges in hormones (i.e., cortisol), which may regulate the adaptive functional changes that occur with the transition to postnatal enteral milk feedings (Carver & Barnes, 1996).

In this study, the rate of cesarean section was significantly higher in the CPG group. Infants in the CPG group may also be further disadvantaged by the lower number of mothers who received antenatal steroids. However, it is difficult to extrapolate from the data what percentage of these cesarean sections were electively performed prior to the
onset of labor as these data were not collected prospectively.

The primary effects of corticosteroids have been studied by examining the effects of antenatal steroids on the ontogeny of gastrointestinal motility, specifically that of the duodenum. Morriss et al. (1986) measured duodenal motility, by intraluminal manometry, in 11 healthy premature infants between 27 to 32 weeks gestation whose mothers had received betamethasone (10 mg at least twice) 24 hours prior to delivery. These measurements were compared to a control group of 15 healthy premature infants whose mothers did not receive betamethasone but were similar in mean gestational age, incidence of cesarean section delivery and fetal distress. The only significant difference was an increased incidence of birth without labor in the group not exposed to betamethasone. Infants whose mothers received betamethasone had an enhanced duodenal contraction rate \( (p = 0.002) \), number of contractions per bursts \( (p = 0.007) \), and intraluminal peak pressure \( (p = 0.015) \). In infants 26 to 29 weeks gestational age, the effect was more marked (Morriss et al., 1986). As previously mentioned, in Chapter 2, it is between 29 and 32 weeks gestation that the number and amplitude of duodenal contractions increase markedly (Milla & Fenton, 1983). Hence, in these infants the changes were noted before the expected onset of spontaneous maturation of duodenal motility (Morriss et al., 1986).

Duodenal activity is an important element in gastric emptying. Intact coordinated motor activity of the fundus, antrum, pylorus, and duodenum are important for effective gastric emptying (Berseth, 1996). The lack of antroduodenal coordination in premature infants has been implicated in delayed gastric emptying (Ittman et al., 1992). Since the
association of antral with duodenal activity appears to be correlated with changes in duodenal motor activity (Ittman et al., 1992), one could postulate that enhanced duodenal activity could result in improved antroduodenal coordination, thereby improving gastric emptying and tolerance to feeds. Given that infants in the Standard Practice group were exposed to antenatal steroids more frequently than infants in the CPG group, it may explain why there was no significant difference between groups in variables related to feeding intolerance including number of feeding interruption, days on TPN, and days to full feeds. As well, there were no significant differences in secondary outcomes of weight gain and age at discharge between infants in the two groups.

Post-hoc analysis undertaken to explore the relationship between antenatal celestone use and the outcomes of this study, excluded all infants who received antenatal celestone from the analysis. Mann-Whitney U test showed no statistically significant difference in days to full feeds (p = 0.9), number of days feeds were interrupted because of feeding intolerance (p = 0.6), days on TPN (p = 0.7), days to regain birth weight (p = 0.5), and age at discharge (p = 0.8). The sample size may have been too small, 15 and 26 in the Standard Practice group and CPG group, respectively, to detect a statistically significant difference. Since the standard of practice is to give celestone in the event of threatened premature delivery, data were re-analyzed after excluding those infants whose mothers did not receive antenatal steroids. The sample size was 85 and 74 for the Standard Practice group and CPG group, respectively. Mann-Whitney U test showed no statistically significant difference in age when feeds were commenced (p = 0.08), days to full feeds (p
number of days feeds were interrupted because of feeding intolerance (p = 0.82),
days on TPN (p = 0.98), days to regain birth weight (p = 0.58), and age at discharge (p =
0.92).

Studies have also examined the secondary effects of corticosteroids, on conditions
such as NEC, in infants whose mothers received corticosteroids. An overview of the
evidence from 12 controlled trials which involved 3000 participants, showed that there is a
decreased risk of NEC with use of antenatal corticosteroids (Crowley et al., 1990). This
systematic review used the Oxford Database of Perinatal Trials to locate all published
reports of randomized controlled trials of corticosteroid use in threatened or planned
premature delivery (Crowley et al., 1990). Although data are limited, they indicate that
the odds of NEC are reduced between 10 and 80% after administration of corticosteroid.
A randomized controlled study, published after this systematic review, done to specifically
determine whether prenatal corticosteroid therapy would reduce the incidence of NEC,
also showed a decreased incidence of NEC after prenatal steroid treatment (Halac et al.,
1990).

Studies examining neonatal outcomes after multiple courses of antenatal steroids
have shown no reduction in incidence of NEC with single or multiple courses of antenatal
steroids (Banks et al., 1999; Vermillion, Soper, & Chasedunn-Roark, 1999). These two
studies differ in their findings to earlier studies which have shown a decrease in the
incidence of NEC after administration of corticosteroids. In both of these studies (Banks
et al., 1999; Vermillion et al., 1999), NEC was a secondary outcome and the studies were
not powered to detect a difference in the incidence of NEC after prenatal administration of corticosteroids.

In this study, there was no significant difference in the incidence of NEC between infants in the SP and CPG groups. Given the use of antenatal steroids was more frequent in the Standard Practice group then the CPG group, this factor confounds the results of this study. Infants in the CPG group, however, were at no greater risk of NEC despite being disadvantaged by the fact that the use of antenatal steroid was lower in this group of infants. The sample size calculation for this study was based on the outcome of days to full feeds. Given the low incidence of NEC, the study lacks sufficient power to detect a difference in the incidence of NEC between the groups and the data should be interpreted with caution.

A systematic review done by Crowley et al. (1990) failed to substantiate the postulation that the risk of neonatal infection may be higher in neonates whose mothers received Celestone after prolonged rupture of membranes. Vermillion et al. (1999) conducted a prospective analysis of infants delivered between 24 and 34 weeks gestation after premature rupture of membranes, to determine the effect of antenatal betamethasone exposure on the incidence of early onset neonatal sepsis. Early neonatal sepsis was defined as having either a positive blood or cerebrospinal culture within the first 48 hours of life, before administration of antibiotics. These researchers compared outcomes of infants categorized into the following groups, no steroid exposure or control (n = 203), single course or two 12 mg doses in a 24 hour interval on admission (n = 99), and multiple
courses or weekly administration after the initial single course (n = 72). Comparisons of
groups revealed a significant increase (p < .0001) in the incidence of early-onset neonatal
sepsis in the multiple-course group, rates being similar between the single course and
control groups. Gram-negative bacteria, particularly Escherichia coli, was predominantly
isolated. Multiple regression analysis using early-neonatal sepsis as a dependent variable,
and including variables determined to be potential risk factors, such as single course of
betamethasone, latency, maternal Group B streptococcal status, and diagnosis of
chorioamnionitis, showed that multiple-dose betamethasone exposure and gestational age
were independently associated with early-onset neonatal sepsis.

In this study, there was no significant difference in the occurrence of infection
between the Standard Practice and the CPG group. However, a wider spectrum of
microorganisms were isolated in blood cultures of infants in the CPG group.

Staphylococcus aureus, Staphylococcus coagulase negative (Staphylococcus epidermidis),
Escherichia coli, Group B Streptococcus and Klebsiella, are the most common
microorganisms responsible for neonatal infection. Some of these organisms are
frequently nosocomial (Kenner & Lott, 1994). Once again, the sample size calculation for
this study was based on the outcome of days to full feeds, hence, the study may lack
sufficient power to detect a difference in the incidence of infection between groups.

7.4 Compliance with CPG

One could infer from the boxplot, figure 7, depicting age when feeds were
commenced, that there was less practice variation in timing of first feed in the CPG group.
In 5% of cases, the first feeding orders were not adhered to by the nursing staff for infants in the CPG group. The CPG may have improved nurses compliance with feeding orders as the failure rate in following a clinician’s feeding order was higher, 25%, for infants in the Standard Practice group. Intuitively, one would expect a significant difference in the study outcomes if there was less practice variation and if nurses were following physicians feeding orders. However, for 60 infants, feeds were not initiated at 48 hours as per guidelines. To explore the relationship between age of commencement of feeds and outcomes of this study, infants in the CPG group who had feeds initiated after 48 hours were excluded from the analysis. The sample size for this post-hoc analysis was 40 and 100, for the CPG and Standard Practice groups, respectively. The Mann-Whitney U test showed a statistically significant difference in number of days on TPN (p = 0.007), and age at discharge from hospital (p = 0.006) in favor of the CPG group. For days on TPN, the median(range) was 12(53) for the Standard Practice group compared to 7(42) for the CPG group. For age at discharge from hospital, the medians(ranges) for the Standard Practice and CPG groups were, 27(182) and 11(79), respectively.

Data on age when feeds were commenced suggest there was failure to comply with CPG. One contributing factor for this noncompliance may have been ethical conflict. Multiple purposes have been proposed for CPG which include improving quality of care, decreasing costs (Battista & Hodge, 1993), reducing variability among practitioners (Redman, 1996), enhancing access to care, patient empowerment, and professional autonomy (Somerville, 1993). Given the multiple purposes of CPG, their development
and use in clinical practice will ultimately involve judgements of obligation and judgements of value. Judgements relating directly to action and concern what we ought to do are termed judgements of obligation, judgements of value concern what is good or has value (Thomas & Waluchow, 1990). Inherent in the development and use of guidelines are values with regard to the research literature, outcomes, and management issues (i.e., economic, social, legal, and administrative rules) regarding CPG. The consensus of experts, which has been the crux of the development of these CPG, may eliminate idiosyncratic judgements of single clinicians; however, it introduces value judgements (e.g., choices made on the basis of evaluation of safety or effectiveness) about what ought to be done for a condition (Battista, Hodge, & Vineis, 1995; Flynn, 1987; Veatch, 1991). The fact that no significant difference was found between the Standard Practice group and CPG group in age when feeds were commenced, suggests that value judgements may have played a role in the implementation of CPG. Understanding these ethical conflicts or dilemmas will help to facilitate implementation or revision of CPG and increase the potential benefit to patients. Studies on CPG need to have a qualitative component which identifies and defines ethical issues, explains ethical judgment or behaviors, and analyzes or appraises clinical decision making.

This study has not examined the impact of CPG on social or cultural outcomes. Anecdotally, however, nurses report more autonomy in practice, and the CPG gave nurses a reference to discuss clinical issues related to feeding. Additionally, new clinicians such as residents and medical/nursing students, use the CPG to help them decide what the
reasonable course of action should be in relation to feeding VLBW infants, and identifying feeding intolerance in this population of infants. Studies evaluating CPG have detected significant improvements in the process of care after the introduction of guidelines, although the size of improvements in performance was variable (Grimshaw & Hutchinson, 1995). A systematic review identified 18 studies which provide evidence that guideline-driven care can be effective in changing the process of care (Thomas et al., 1999). Of particular importance were six studies (Franz et al., 1995; Frigoletto et al., 1995; French, Cheng, Wong, & Donnan, 1989; Naylor, 1990; Naylor et al., 1994; Shaffer & Wexler, 1995) which observed improvements in outcomes of care. Behaviors examined included nutrition therapy for non-insulin-dependent diabetics (Franz et al., 1995), management of labor (Frigoletto et al., 1995), discharge planning (Naylor, 1990; Naylor et al., 1994), lipid lowering (Shaffer & Wexler, 1995) and infection control (French et al., 1989). Outcomes which showed an improvement after the introduction of guidelines included lipoprotein cholesterol levels (Franz et al., 1995; Shaffer et al., 1995), triglyceride level, weight (Franz et al., 1995), duration of labor and maternal fever (Frigoletto et al., 1995), post-discharge infection rates (Naylor, 1990), rehospitalization rates (Naylor, 1990; 1994), total days rehospitalized (Naylor, 1994), hospital discharge (Naylor, 1994), and hospital-acquired urinary tract infections (French et al., 1989).

All but one study (Franz et al., 1995) was targeted at nurses; physicians were not represented in any of these studies. All studies had inadequate reporting methods (Thomas et al., 1999). The methodological quality varied and included randomized
controlled trials (e.g. Franz et al., 1995), interrupted time series (e.g. French et al., 1989), and controlled before and after studies (e.g. Shaffer & Wexler, 1995). None of the studies adequately reported study methods or assessed for sustained change in performance or outcomes (Thomas et al., 1999). In addition, the studies were not intended to evaluate the introduction of guidelines targeting nurses and physicians working in an NICU setting. In fact, Thomas et al. warn against interpreting the findings from their review and in generalizing these findings to other professions and settings. Consequently, a study needs to be done which evaluates the impact of these guidelines on the process and outcomes of care in the NICU.

7.5 Relationship Between Confounders and Study Outcomes

A multiple stepwise linear regression analysis was carried out in order to establish a relationship among days to full feeds and various confounders discussed above, including gestational age, mode of delivery, maternal antenatal celestone, prolonged rupture of membranes, indomethacin, erythromycin, cisapride, age when feeds were commenced, and study period. The number of ventilator days and the number of feeding interruptions related to feeding intolerance were also included in the regression analysis. These two variables were significant predictors for days to full feeds (F(2,55)=35.81, p>0.001) in a pilot study conducted in a 33 bed, university-affiliated teaching hospital, NICU to delineate standard practice (details of the study are presented in Appendix A).

Infants in both groups, Standard Practice and CPG, were included in the multiple stepwise linear regression analysis, however, because infants with missing data were
excluded from the analysis, the subject number for the analysis was 138 infants. The analysis demonstrated that the number of days feeds were interrupted for feeding intolerance, number of ventilation days, and use of cisapride for feeding intolerance were significant predictors for days to full feeds (F(3, 134)=98.3, p<0.0001). The model explained 69% of the variance in days to full feeds. The number of days feeds were interrupted for feeding intolerance contributed 66% to the model, while number of ventilation days and use of cisapride contributed 2% and 1%, respectively. Although the multiple stepwise linear regression analysis failed to establish compliance with CPG as a significant predictor for days to full feeds, the true estimate of the effect of this variable may be limited by the sample size.

Because of the finding of no difference between groups, a post-hoc power analysis was undertaken to minimize the possibility of a Type II error. The mean and standard deviations for days to full feeds of each group, Standard Practice and CPG, were used to estimate the power. The power for this study was 0.15 which is well below the accepted standard convention of 0.8, hence, it would not be prudent to conclude that the intervention, that is, implementation of CPG, has no merit. The low power of this study may be explained by the fact that the sample size calculation for this study was based on a t-test for unpaired samples. A sample size, based on a power of 0.8, 2-tailed test for paired samples, alpha level of 0.05, of 900 pairs of infants is needed to ensure that a Type II error, or incorrectly accepting a false null hypothesis, is not committed.
7.6 Study Implications

7.6.1 Practice implications

Although this study showed no significant difference in outcomes between the Standard Practice and CPG groups, the CPG did provide clinicians with a framework (Pare & Freed, 1995) to assess readiness to feed, investigate the variance from an established norm, for example feeding intolerance, and to identify strategies for management of feeding intolerance. Additionally, the CPG did not impede the clinical outcomes of infants in the CPG group. Consequently, the use of these CPG may still be warranted in practice. It is imperative, however, that clinicians understand the values with regard to the research literature, outcomes, and management issues (i.e., economic, social, legal, and administrative rules) regarding CPG (Battista et al., 1995; Flynn, 1987; Veatch, 1991). If clinicians lack this understanding, then ethical conflicts or dilemmas could ensue which may impede the adoption of CPG (Redman, 1996). Additionally, CPG may not be appropriate for all premature infants, for example those who have received indomethacin therapy, hence clinicians need to exercise judgement otherwise they may compromise the infant’s care. From an ethical point of view CPG would only indicate the conduct recommended and would not be definitive (Somerville, 1993). According to Somerville, “it is the nature, privilege and responsibility of a profession that there be an exercise of individual and independent judgement in each case in which a professional is involved” (p. 1134).
7.6.2 Policy implications

Many units grappling with restructuring may be inclined to implement guidelines without consideration for the social process involved in behavior change. Simply adopting guidelines will not ensure that they will be implemented. Implementation strategies which comprise processes aimed to improve the clinician’s compliance with the recommendations (Grimshaw & Huchinson, 1995) will determine the extent to which CPG are useful. Although strategies, such as opinion leaders and in-services, employed in this study are effective methods of disseminating guidelines and improve compliance (Seto, Ching, Yuen, Chu, & Seto, 1991), the implementation process is the most difficult step (Clarke, 1996). In this study, age when feeds were commenced was used as an indicator of compliance and no significant difference was found between groups. The theoretical framework, Rogers’ theory (1983), used to implement the CPG in this study applies to decisions made by a single individual. The theory does not focus on the individual’s response to sociopolitical influences, for instance, the complex nature of the present health care system. Rogers’ theory assumes that the target system, clinician, physician or nurse, is natural and there are no driving or restraining forces within it. It assumes that the process is linear and that actions are purposive, intentional, goal directed and rational (Romano, 1990). Rogers’ theory (1983) assumes that clinicians have a choice of adopting or rejecting change. In reality, clinicians may or may not have a choice. There is no literature on how organizational circumstances influence the impact of CPG on changing clinicians’ behavior. A multifactorial approach which includes strategies targeted at the
individual, social structure, policy, and management, is necessary to ensure compliance with CPG.

An infrastructure in which data related to process, outcomes, and cost measures, can be tracked would be extremely useful in evaluating CPG (Johanson, 1998). For example, a computerized nursing charting system which requires nurses to enter clearly defined variables related to feeding intolerance, incorporating what they already do in practice, will ensure accurate collection of data which can be easily accessed. In this study, the documentation system changed part way through the study. The impact of this change in documentation remains unclear.

This study did not include a cost analyses because of time constraints, lack of money and resources. Given current fiscal restraints, it is essential that new innovations, such as CPG, provide maximum benefit for their cost. The magnitude of the resultant benefits and costs must be determined systematically and nonarbitrarily (Emery & Schneiderman, 1989).

7.6.3 Implications for future research

Given the current state of scientific knowledge, described in Chapter 3, related to various areas of nutritional management for premature infants, it is essential to determine whether the implementation of these CPG improves or worsens outcomes for premature infants < 1500 grams. Future research needs to adopt a stringent study design, for instance a multi-center controlled trial, stratified for birth weight, to study the efficacy and safety of CPG for feeding premature infants < 1500 grams. A controlled study design will
ensure that confounding variables, for example antenatal steroid use and rate of cesarean section deliveries, are equally distributed between the Standard Practice and CPG groups. Stratification by gestational age and birth weight will ensure that there is representation of infants at varied stages of development of the gastrointestinal system. Furthermore, studies need to measure the relative effectiveness of CPG. Emphasis on effectiveness will allow the researcher to evaluate the utility of guidelines in practice, process of care, quality of care, and patient/parent satisfaction (Johanson, 1998). This is particularly important given the monetary cost which can be incurred in the development of guidelines. A study which focuses on effectiveness will ensure that the CPG provide the maximum benefit for their cost (Johanson, 1998).

This study focused on short-term outcomes, though nutrition during a critical period in early life can have long-term neurodevelopmental consequences (Morley & Lucas, 1993). Studies examining the effect of early nutrition should focus on outcomes such as long-term neurodevelopmental performance, growth and morbidity in childhood (Lucas, 1990). CPG may pose a substantial advantage to premature infants in long-term neurodevelopmental outcomes which can consume significant community resources. Future studies need to appraise the impact of CPG on later growth, development and disease in later life. Future studies also need to focus on various areas of nutritional management for premature infants including:

1. Feeding during indomethacin therapy for closure of PDA. A randomized controlled trial needs to evaluate the benefits of feeding versus not feeding during the course of
indomethacin therapy.

2. A systematic review needs to be undertaken to examine the evidence regarding the effectiveness of continuous versus intermittent nasogastric bolus tube feeding in premature infants less than 1500 grams.

Since the lack of difference in this study may be reflective of the ontogeny of the gastrointestinal system, effects of gestational age and illness severity on stooling pattern need to be established. The impact of stooling patterns on feed tolerance needs to be explored. As well, the role of glycerine suppository, and rectal washouts in the management of feeding intolerance needs to be examined.

7.7 Conclusion

Although this before-after study failed to show that CPG for feeding premature infants < 1500 grams were efficacious, CPG did not impede outcomes, that is, they were safe. Intention-to-treat analysis was used to evaluate the efficacy and safety of CPG, despite the fact that CPG were not always being adhered to in practice. Ethical conflicts or dilemmas resulting from values inherent in the development of guidelines may explain why CPG were rejected. It is imperative that CPG be implemented consistently in practice to ensure that study findings are meaningful. In this regard, a multifactorial approach which includes strategies targeted at the individual, social structure, policy and management, is necessary to ensure compliance with CPG. A more rigorous study design, such as a multi-center controlled trial, is needed to ensure that confounding variables, for example immaturity of the infant, antenatal steroid and indomethacin use, are equally
distributed between infants in the Standard Practice and CPG groups. The study design should include measurement of relative effectiveness of CPG in order to evaluate the utility of the guidelines, process of care, quality of care, and parent/patient satisfaction. Additionally, outcome measurements should include long-term neurodevelopmental performance, growth and morbidity in childhood. A comprehensive assessment will provide means to systematically and nonarbitrarily appraise the magnitude of the resultant benefits and costs of CPG for feeding premature infants < 1500 grams.
References

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Appendix A

Title: Variation in Feeding Practices for Premature Infants Less Than 1500 Grams:
Impetus for Clinical Practice Guidelines

Principal and Corresponding Author:
Shahirose S. Premji, Ph.D.(candidate)
Clinical Nurse Specialist/Neonatal Practitioner
Acute Children’s Services, Children’s Hospital Neonatal Unit - MUMC 4G
Hamilton Health Sciences Corporation (HHSC)
1200 Main St. West, Hamilton, Ontario, CANADA L8N 3Z5
Telephone (Business): (905) 521-5025
Telephone (Home): (905) 828-7411
Fax: (905) 521-5007
E-mail: Premji@hhsc.ca

Co-Authors:
Lori Chessell, BSc, RD, Acute Children’s Services, HHSC
Dr. B. Paes, F.R.C.P.(I), F.R.C.P.(C), Chief of Neonatology, St. Joseph’s Hospital,
Professor in the Department of Pediatrics (Neonatal Division), HHSC
Dr. J. Pinelli, DNS, McMaster University, School of Nursing and Clinical Nurse
Specialist/Neonatal Practitioner, Children’s Hospital, HHSC
Dr. K. Jacobson MB. Bch., F.R.C.P.(C), Gastroenterologist, Department of Pediatrics,
B.C. Children’s Hospital

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Key words

Feeding practices

Very low birth weight infants

Clinical practice guidelines
Abstract

Objectives: The objective of this descriptive study was to delineate feeding practices for premature infants < 1500 grams and to determine the impact of these practices on the number of days to establish full feeds.

Study Design: Chart reviews were conducted for all appropriate for gestation age infants < 1500 grams without major congenital anomalies, admitted to the NICU (n=58). Prenatal history, mode of delivery, clinical status of the infant, and feeding variables impacting on days to full feeds were collected from the day of admission until 48 hours after tolerance of full feeds or discharge from hospital. Feeding variables examined included timing of first feed, feeding orders, whether prescribed orders were actually implemented, and number of days feeds were interrupted.

Results: Variability was evident in all practices and feeding outcomes evaluated. Multiple linear regression analysis demonstrated that the number of ventilator days and the number of feeding interruptions related to feeding intolerance were significant predictors for days to full feeds (F(2,55)=35.81, p>0.001). The model explained 57% of the variance in days to full feeds.

Conclusion: Differences in practice including timing of first feed, management of feeding intolerance, and clinical status of the infant, may explain the variability identified.
A premature infant born weighing less than 750 grams has a less than 40% chance of survival. The overall survival rate improves with increasing birth weight; the largest impact however, has been in infants weighing less than 750 grams. Providing nutritional support to the increasing number of survivors has been challenging for a number of reasons: (a) lack of evidence based scientific data about when, and how to feed premature infants; (b) limited clinical experience; and (c) wide variation in practice. Hormonal, anatomic, and functional limitations of these small premature infants and the effect of critical illness further complicate feeding decisions in this population.

Although infant nutrition remains a widely researched area in pediatrics, a great deal of uncertainty exists in the approach to feeding small preterm infants. Most studies have focused on short-term outcomes such as growth. These studies have not rigorously controlled for confounding variables such as underlying disease states or patent ductus arteriosus and have methodological limitations, such as small sample sizes. Consequently, the body of valid research in the area of feeding small preterm infants is plagued by inconsistent and controversial findings, leading to large variation in practice.

The objectives of this study were to describe the feeding practices and clinical outcomes of premature infants less than 1500 grams, and determine the impact of these practices on the number of days to establish full feeds.

**Methods**

**Study Setting, Population, and Design**

The study was conducted in a 33-bed neonatal intensive care unit (NICU) in a
university affiliated teaching hospital, between February 1997 and August 1997 and involved all premature infants less than 1500 grams. The average number of admissions per year is 800 to 1000, the majority of whom are in-born. Approximately 20% of these admissions are infants weighing less than 1500 grams at birth. Two teams of clinicians, resident and clinical nurse specialist/neonatal practitioner (CNS/NP) team, provide care to the infants and families. The resident team, is supervised by a neonatal fellow and each team is accountable to an attending neonatologist. The residents rotate through the NICU every 2 months and the attending neonatologist changes every month. A total compliment of 10 CNS/NPs, 7 neonatologists, and an average of 4 neonatal fellows work in the NICU. Each clinician prescribes feeding regimens for infants under their care, while a dietitian, overlooks the feeding management of all infants in the unit.

The nursing staff consists of 109 registered nurses whose experience and knowledge range from novice to expert, and who practice primary care nursing. Emphasis is placed on family-centered care with an appreciation of the diversity of cultural, educational and socioeconomic backgrounds of infant’s families.

Feeding practices were evaluated in 58 infants out of a total number of 102 admissions during the study period. Infants born with a maternal history of drug use during pregnancy, chromosomal abnormalities, major congenital anomalies, particularly of the gastrointestinal tract, or intrauterine growth restriction were excluded from the study a priori.

Chart reviews were conducted on all study infants. Prenatal history, mode of
delivery, clinical status of the infant, and feeding variables impacting on days and age to full feeds were collected. Feeding variables examined included timing of first feed, feeding orders, whether orders were actually implemented, and number of days feeds were interrupted. Data collection began on the day of admission and continued for 48 hours after tolerance of full feeds or discharge from hospital.

Informed Consent

This study embodied continuous quality management by evaluating clinical practice and identifying problems. Informed consent was not deemed necessary because the focus was on quality improvement rather than the evaluation of an intervention. The Research Ethics Board of the institution found the study to be acceptable on both clinical and scientific grounds.

Data Analyses

Infants were stratified into three weight categories: less than and equal to 749 grams, 750 to 999 grams, and 1000 to 1499 grams. The data are expressed as mean and standard deviations unless otherwise stated. The data on the total number of days feeds were interrupted includes all interruptions in feeds, regardless of the number of feeds held and the cause. Feeding intolerance was defined as three or more feeds held at any time, consecutive or nonconsecutively, in a 24-hour period because of residuals, vomiting, or abdominal distention. Data collection ceased only if infants developed proven necrotizing enterocolitis (NEC) (modified Bell staging IIA to IIIB7). Infants were not followed once they were discharged from the NICU regardless of whether or not they had reached full
feeds. Multiple linear regression analysis was done to identify predictors for days to full feeds.

Results

The clinical characteristics of infants in each of the weight categories is summarized in Table 1. Wide variation in practice was demonstrated for all weight groups in timing of first feed, feeding orders, volume and frequency of feed increases, and whether orders were actually implemented. Feeds were interrupted for various reasons including feeding intolerance.

**Infants less than and equal to 749 grams.** There were six infants in this weight category (see Table 1). One infant developed NEC with a perforation on day 5 of life after receiving only one feed. Data from this infant were included only in the analysis of timing of the first feed, which was $6 \pm 1.8$ days. The first feed order for all infants was 1cc every 6 hours with no increase on the first day. In 14% of cases, feeding orders were not followed either because the nurses felt the increases ordered were too slow or too fast, or because the feeds had to be interrupted for reasons other than intolerance (for example, blood transfusion, starting of intravenous lines, and procedures such as intubations and lumbar punctures). Table 2 summarizes the number of days feeds were interrupted, including interruptions related to intolerance and other causes, and those solely for feeding intolerance. Variability was also noted in feeding outcomes for days to full feeds and age at full feeds (see Table 2).

**Infants 750 to 999 grams.** There were 16 infants in this weight category (see
Table 1). One infant developed intestinal perforation secondary to NEC on day 10 of life. Data from this infant were included in the analysis of timing of first feed and excluded in the analysis of days to full feeds, and age at full feeds. This infant’s feeds were initiated on day 3 of life and because of feeding residuals and abdominal distention, the feeds were discontinued on day 5 of life.

The timing of the first feed in this cohort of infants was 4.7 ± 3 days. The first feeding order was variable and included 1cc every 4, 6, 8, or 12 hours or 2cc every 2 or 4 hours (see Table 2). The most frequent feeding order (n=7) was 1cc every 6 hours with no feed increase. The exception was one infant who had an order for feed increase of 1cc every 12 hours. The analysis revealed that in 20% of cases, feeding orders were not followed in practice. In some instances, the nurses felt that the increases ordered were too slow and therefore, increased the feeds faster. In other cases, the nurses felt the feed itself or the increase in feed ordered would not be tolerated; hence, feeds were either not increased, increased slower than ordered, or interrupted. Feeds were interrupted for several reasons other than feeding intolerance (for example, indomethacin therapy, poor capillary blood gas, tachypnea, blood transfusion, apneic and bradycardic episodes, getting the infant back on the handling schedule, or the nurse recognizing that the infant had been stressed from other procedures). The number of days from the start of feeds to full feeds varied among infants resulting in variability in age at full feeds (see Table 2).

**Infants 1000 to 1499 grams.** One of the 36 infants in this weight category (see Table 1) was suspected of having NEC. The timing of the first feed was 3.3 ± 1.7 days.
The first feeding order in this group was variable and included 1cc every 2, 4, 6, or 8 hours; 2cc every 2, 4, or 6 hours; 3cc every 3 hours, or 6cc every 3 hours. The majority of infants (n=26) had no increases ordered with the first feed. When increases in feeds were ordered, they included, 1cc every 6, 8, or 12 hours; 2cc every 2, 6, 8, or 12 hours; or 3cc every 9 or 12 hours. The analysis revealed that in 37% of cases, feeding orders were not followed in practice. The reasons were similar to those cited previously. Feeds were interrupted because of feeding intolerance and other reasons (for example, aspiration, line insertion, blood transfusion, tachypnea, large amounts of air in the stomach, possible sepsis, thrombocytopenia, apnea resulting from sedation for computerized tomography scan). Once again, variability was noted in days to full feeds and age at full feeds (see Table 2). Thirteen infants were transferred to referral hospitals prior to reaching full feeds.

Management of Feeding Intolerance for all weight categories

The strategies used to manage feeding intolerance were inconsistent across all weight categories of infants. Management approaches included decreasing the volume of feed and/or increasing the time interval between feeds, or holding feeds. The number of days feeds were held depended upon the clinical status of the infant, the number of episodes of feeding intolerance, x-ray findings if available, and the comfort level of the caregivers. In some instances, cisapride, was commenced. The number of infants on cisapride was one in the ≤ 749 grams weight category (n=6), five in the 750 to 999 grams category (n=16), and one in the 1000 to 1499 grams category (n=36). In accordance with
Janssen Pharmaceutica's safety recommendations, the use of cisapride in premature infants less than 1500 grams early in the postnatal course was discontinued, on September 10, 1997, after the study period.

**Predictors for days to full feeds**

Differences in practice including timing of first feed, management of feeding intolerance, and clinical status of the infant, may explain the variability noted in days to full feeds (see Table 2 for the respective weight categories). Multiple linear regression analysis on infants in all weight categories, demonstrated that the number of ventilation days and feeding interruptions related to feeding intolerance were significant predictors for days to full feeds ($F(2, 55)=35.8$, $p<0.001$). The statistical model explained 57% of the variance in days to full feeds, with 47% of the contribution from ventilation days and 10% from feeding interruptions related to feeding intolerance.

**Discussion**

Wide variation in practice exists in the nutritional management of premature infants less than 1500 grams. These variations in practice may explain the differences noted in outcomes of days to full feeds and age at full feeds. Our data suggest that the number of ventilation days and feeding interruptions related to feeding intolerance partly explains the variance in the number of days it takes infants to reach full feeds. Feeding interruptions related to feeding intolerance explained only 10% of the variance. However, the true estimate of the effect may be limited by the small sample size.

Our data also indicated that there was great variability in timing of first feed, and
feeds were initiated as late as day 14 of life in the 750 to 999 grams weight category.

There were 4 infants who had feeds initiated after the first week of life. Current research suggests that minimal enteral nutrition (MEN), feeding small amounts of enteral feeds soon after birth, achieves biologic effects\(^8\) such as increases in plasma concentration of gut hormones,\(^9\) maintenance and development of structural and functional characteristics of the gastrointestinal tract,\(^10\) promotion of intraepithelial lymphocyte expansion,\(^11\) and enhancement of gastrointestinal motility.\(^12\) Consequently, MEN is likely important in gut development and postnatal adaptation. Although the multiple linear regression analysis failed to establish timing of feeds as a significant predictor for days to full feeds, one could postulate that timing of feeds may influence the infant's ability to tolerate feeds, thereby, indirectly influencing days to full feeds.

The practice of withdrawing feeding to check for residual was consistent among caregivers. However, the management of feeding residuals was variable, and, depending on the type (mucus or partially digested) and/or amount of residual, it was refed or discarded. Disparities were noted within and among nurses. Some nurses always either refed or discarded residuals, while others did not always handle residuals in the same way from feed to feed, regardless of type or amount of residual. Infants’ feeds were sometimes held or not restarted for undetermined reasons. The non-unified approach to the management of feeding residuals and feeding intolerance, as demonstrated in this study, leads to inconsistency in the provision of care which may impact on feeding outcomes.

Even more concerning is the fact that in 14 to 37% of the cases, feeding orders
were not adhered to by the nursing staff. The failure rate in following physicians feeding orders was higher for infants between 1000 to 1499 grams. Intuitively, one would expect a higher failure rate with infants less than 749 grams because these infants would have more confounding variables (e.g., patent ductus arteriosus), and caretakers would have more discomfort in feeding these infants. However, this was not the case. One could postulate that nurses were less likely to digress from feeding orders in the less than 749 grams weight category of infants because of the uncertainty about clinical state and implications for feeding. In contrast, with older infants who were clinically more stable or had less confounding variables, they would feel more comfortable using their discretion about amending feeding orders.

Given the number of clinicians (medical and nursing) involved in the nutritional management of infants less than 1500 grams in our unit, it is not surprising that there is great variability in practice. The inconsistencies in feeding practices in our unit maybe reflective of feeding practices in other NICUs which have multiple care providers. It is imperative that feeding practices in all NICUs be critically appraised to ensure that they are consistent with current knowledge of gastrointestinal ontogeny and research in the area of nutritional management for infants less than 1500 grams. A unified approach that is research-based is necessary to eliminate inappropriate variation in practice.

CPGs are one strategy to address the challenges of feeding small premature infants because they are evidence-based, and may limit inappropriate variation in practice.\textsuperscript{13} CPGs attempt to "refine decision making and to narrow practice variation to a degree
unlikely to be achieved ‘naturally’ by the target audience(s).” Additionally, the guidelines will assist medical and nursing practitioners with limited clinical experience in making decisions about appropriate nutritional management of premature infants. Since there is little evidence about the effectiveness of CPGs in a NICU setting, evaluation of the implementation of such a clinical policy is needed. If CPGs are implemented in practice, it is crucial to study the efficacy and safety of these guidelines for feeding premature infants less than 1500 grams birth weight.
References


Table 1 Clinical Characteristics of infants

<table>
<thead>
<tr>
<th></th>
<th>≤ 749 grams (n=6)</th>
<th>750 - 999 grams (n=16)</th>
<th>1000 - 1499 grams (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td>25.0 ± 0.9</td>
<td>26.3 ± 1.3</td>
<td>29.1 ± 1.6</td>
</tr>
<tr>
<td><strong>Birth Weight</strong></td>
<td>676 ± 66</td>
<td>894 ± 88</td>
<td>1239 ± 142</td>
</tr>
<tr>
<td><strong>Apgar, 1 minute</strong></td>
<td>5.7 ± 2.3</td>
<td>5.7 ± 2.4</td>
<td>6.6 ± 1.8</td>
</tr>
<tr>
<td><strong>Apgar, 5 minute</strong></td>
<td>7.3 ± 0.8</td>
<td>7.9 ± 1.6</td>
<td>8.2 ± 0.9</td>
</tr>
<tr>
<td><strong>Oxygen (days)</strong></td>
<td>73.7 ± 40.4</td>
<td>36.7 ± 25</td>
<td>9.2 ± 17.2</td>
</tr>
<tr>
<td><strong>Ventilation (days)</strong></td>
<td>51.5 ± 28.5</td>
<td>25.2 ± 14.9</td>
<td>5.4 ± 11.6</td>
</tr>
<tr>
<td><strong>NP CPAP (days)</strong></td>
<td>10.5 ± 6.4</td>
<td>10.9 ± 8.4</td>
<td>4.9 ± 5.9</td>
</tr>
</tbody>
</table>

Data are represented as Mean ± Standard Deviation
NP CPAP = Nasal prong continuous positive airway pressure
### Table 2. Summary of Analysis

<table>
<thead>
<tr>
<th>Age(days) when feeds commenced</th>
<th>Number of days feeds interrupted</th>
<th>Number of days feeds interrupted for feeding intolerance</th>
<th>Days to full feeds</th>
<th>Age(days) at full feeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 749 grams</td>
<td>n=6</td>
<td>n=5*</td>
<td>n=5**</td>
<td>n=4**</td>
</tr>
<tr>
<td>6 ± 1.8</td>
<td>5.6 ± 2.6</td>
<td>2.8 ± 1.9</td>
<td>28.2 ± 15.5</td>
<td>34.8 ± 13.7</td>
</tr>
<tr>
<td>4 - 9</td>
<td>1 - 7</td>
<td>0 - 5</td>
<td>18 - 51</td>
<td>25 - 55</td>
</tr>
<tr>
<td>750 - 999 grams</td>
<td>n=16</td>
<td>n=16</td>
<td>n=16*</td>
<td>n=15*</td>
</tr>
<tr>
<td>4.7 ± 3.0</td>
<td>6.4 ± 4.4</td>
<td>3.2 ± 2.7</td>
<td>17.7 ± 6.9</td>
<td>22.6 ± 9</td>
</tr>
<tr>
<td>2 - 14</td>
<td>0 - 13</td>
<td>0 - 7</td>
<td>7 - 30</td>
<td>9 - 38</td>
</tr>
<tr>
<td>1000 - 1499 grams</td>
<td>n=36</td>
<td>n=36</td>
<td>n=36</td>
<td>n=23*</td>
</tr>
<tr>
<td>3.3 ± 1.7</td>
<td>3.1 ± 4.7</td>
<td>1.7 ± 3.1</td>
<td>12.5 ± 8.2</td>
<td>16.4 ± 9.4</td>
</tr>
<tr>
<td>1 - 9</td>
<td>0 - 22</td>
<td>0 - 12</td>
<td>2 - 33</td>
<td>4 - 42</td>
</tr>
</tbody>
</table>

n = sample size
Data are represented as Mean ± Standard Deviation followed by the minimum and maximum value
* = one infant excluded due to perforated NEC
^ = infant(s) that were transferred to referral hospitals prior to reaching full feeds were not included in analysis
~ = one infant developed NEC on day 10 of life, have included data prior to perforated NEC. This infant had feeds interrupted initially (2 days) and then was placed NPO for 5 days before developing perforated NEC.
Appendix B-1

January 18, 2000

Judyann Silbo  
Permissions Coordinator  
Neonatal Network

Dear Ms. Silbo:

I am completing a Ph.D. thesis at McMaster University entitled "Feeding Practice Guidelines for Premature Infants Less Than 1500 Grams: Efficacy and Safety". I would like to request permission to reprint the following articles in my thesis. Additionally, I would like permission to reprint or adopt tables for this thesis. I am the sole or principal author of these articles.


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Sincerely,

[Signature]

Shahirose S. Premji, Ph.D.(c)  
Clinical Nurse Specialist/Neonatal Practitioner  
Hamilton Health Sciences Corporation  
Children’s Hospital Neonatal Unit - MUMC 4G  
1200 Main St. West  
Hamilton, Ontario  
L8N 3Z5  
Phone: (905) 521-5025  
Fax: (905) 521-5007  
E-mail: premj@hhsc.ca

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February 1, 2000

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Children's Hospital at Hamilton Health Sciences Corporation is affiliated with the Faculty of Health Sciences, McMaster University
Ontogeny of the Gastrointestinal System and its Impact on Feeding the Preterm Infant

Shahirose S. Premji, RN, MSc(N)

CURRENT KNOWLEDGE OF GASTROINTESTINAL ontogeny, particularly the effects of the intrauterine and extrauterine environment upon that process, may allow for optimal feeding regimens to be established.1-4 For instance, premature infants with delayed gastric emptying frequently present with feeding intolerance. There may be a relationship between gastric emptying and gestational age, or milk composition, or timing of feedings. Manipulating the various components of what is being fed may be one strategy for improving feeding tolerance of premature infants.1 It is imperative that proposed strategies maintain gut function and integrity. Rational decision making regarding the unique nutritional management of preterm infants may decrease such gastrointestinal pathologies as necrotizing enterocolitis. Additionally, it is hoped that the limitations in our current knowledge of gastrointestinal ontogeny will prompt further research and contribute to the body of knowledge regarding the nutritional management of premature infants. This article focuses on (1) the anatomy of the stomach, (2) the ontogeny of gastric digestion (excluding intrinsic factor), (3) the ontogeny of motor function, and concludes by elucidating the application of this knowledge to clinical practice.

ANATOMY OF THE STOMACH

Macroscopic Appearance
The stomach develops from the endoderm at about 4 weeks gestation.2,3 The endoderm becomes the epithelium and is supported by the mesoderm. The mesoderm is thought to be responsible for epithelial differentiation and expression of digestive enzymes.3 By 6 weeks gestation, the greater and lesser curvatures of the stomach have formed. At the same time, the midgut, consisting of the small intestine and the proximal colon, elongates at a rapid rate. As the midgut loop develops, it herniates into the extraembryonic coelom4 and by the twelfth week returns into the abdominal cavity.3 During this return, the midgut rotates, achieving the mature orientation of the small intestine and colon (Figure 1).3 Over the subsequent weeks, the villous architecture appears.5 By approximately 20 weeks gestation, the macroscopic appearance of the stomach is similar to that of the term infant (Table 1).1

ABSTRACT

The nutritional management of premature infants is a challenging area for neonatal clinicians for a number of reasons. These include lack of knowledge about when, what, and how to feed; limited clinical experience; and wide variations in practice. New practices in the nutritional management of premature infants must take into consideration the structural and functional maturity of the gastrointestinal system and environmental influences on this system.1 This article presents current knowledge of embryology and ontogeny of the premature infant’s gastrointestinal system and explains how this knowledge may be applied to clinical practice.

Microscopic Appearance
From 11 weeks gestation, parietal cells appear. These cells are initially located in the body and antrum of the stomach.

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G cells become more numerous. G cells are most abundant between 26 and 36 weeks gestation.

Gastric acid secretion is also modulated by epidermal growth factor (EGF), a small polypeptide, which inhibits the release of hydrochloric acid by parietal cells. EGF is found in amniotic fluid, and the amount increases with gestational age. An increased number of EGF receptors has been found in the fetus swallowing large volumes of amniotic fluid containing EGF. The EGF receptors were demonstrated to be localized in the luminal aspect of the gastric mucosa. Receptors for EGF are present in the stomach from 18 weeks gestation. EGF may protect the stomach mucosa from acid damage, and may play a role in growth and maturation of the small intestine. Additionally, EGF stimulates DNA and protein synthesis and, therefore, may have an important effect on mitogenesis in the growing gastrointestinal system. EGF may facilitate the adaptation from intruterine to extruterine nutrition because of its antisercretory, cytoprotective, and mitogenic effects on the growing gastrointestinal tract.

From 18 weeks gestation, chief cells demonstrate the presence of pepsinogens, which are important in protein digestion. By about 20 weeks gestation, the fetal stomach is microscopically similar to that of the term infant (Table 1).

ONT GENY Of Gastric Digestion (Excluding Intrinsic Factor)

Both acid and pepsin are important for digestion. Gastric acid activates pepsinogen to form pepsin, an active enzyme necessary for cleaving protein molecules. Pepsin activity has been observed in the stomach of very low birth weight (VLBW) infants. Although hydrochloric acid has been found in the fetal stomach from 19 weeks gestation, it is not known how much acid the fetus produces in situ. Kelly and associates demonstrated that premature infants of 24 to 29 weeks gestation were able to secrete gastric acid; the intragastric pH on the first day of life was higher for the lower-gestational-age infants than for infants of higher gestational age (It was 3.7, 2.5, and 1.8 for infants of 24 to 25, 26 to 27, and 28 to 29 weeks gestation, respectively.) By the third week of life, all infants, irrespective of gestational age at birth, were able to maintain a gastric pH below 2. Thus, with
TABLE 1: Microscopic and Macroscopic Development of the Stomach

<table>
<thead>
<tr>
<th>Development</th>
<th>Stomach develops</th>
<th>Greater and lesser curvature of stomach</th>
<th>Stomach has returned into abdominal cavity</th>
<th>Vilous architecture appears</th>
<th>ATPase pump in situ for PC to secrete acid</th>
<th>Similar to term infant</th>
<th>Similar to term infant</th>
<th>G cells found</th>
<th>G cells most abundant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic appearance</td>
<td></td>
<td>Midgut elongates rapidly and herniates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic appearance</td>
<td></td>
<td>Parietal cells (PC) appear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increasing postnatal life, lower-gestational-age infants secrete more acid. No evidence of diurnal rhythm was found in the pH recordings of these VLBW infants. Adults commonly show a diurnal rhythm in pH recordings. The consequence of the absence of such a rhythm in VLBW infants is unknown. However, it may represent a stage of development, that is, the rhythm develops over time.

From 11 weeks gestation, the fundal region of the stomach secretes gastric lipase (acid stable), which is important in the initial hydrolysis of dietary triglycerides. Lipolytic activity is present in infants as young as 23 weeks gestation. Peak lipolytic activity in gastric aspirates has been demonstrated at 30 to 32 weeks gestation, after which time lipolytic activity decreases again until term gestation. Changes in lipolytic activity at different gestational ages may represent the actual developmental profile of lipolytic activity. It has been postulated that peak levels at 30 to 32 weeks gestation represent a combination of lingual and gastric lipase. Lipase in the lingual gland begins to disappear with increasing gestational age. In adults, gastric lipase predominates, and there is a reduction in total lipase content in the stomach. Comparison of lipolytic activity profiles of infants born at different gestational ages and infants at different postconceptional ages showed similar patterns. The similarity in lipolytic activity profiles suggests that the environment (for example, exposure to multiple drugs) has little effect on the developmental profile of lipolytic activity, which is essential for normal digestion of fat to occur.

ONTODYGEN OF MOTOR FUNCTIONS

The gastrointestinal tract has a muscle coat consisting of two layers—the inner circular layer and the outer longitudinal layer. Early in gestation, layers of smooth muscle develop, in a cranio-caudal pattern, in the mesenchymal layer surrounding the bowel lumen. The circular muscle layers develop before the longitudinal muscle layers. During the fifth week of gestation, the circular muscle layers of the esophagus and stomach become recognizable, but the longitudinal muscle layers do not appear until 8 weeks gestation. The circular muscle layers of the ileum become recognizable by 8 weeks gestation, but the longitudinal muscle layers are not present until 10 weeks gestation. Each muscle layer thickens with increasing gestational and postnatal age. At 25 weeks gestation, the intraluminal contraction pressure amplitudes approach 60 percent of the values noted at term. Consequently, at 25 weeks gestation, the premature infant can generate amplitudes of contractions capable of moving nutrients forward in the gastrointestinal tract.

Four aspects of motor function—coordinated sucking and swallowing, increased lower esophageal pressure, gastric emptying, and intestinal transit—are important when considering enteral nutrition. The first three aspects of motor function are bypassed by giving premature infants oro- or nasogastric, or transpyloric feedings. However, delayed gastric emptying in premature infants frequently presents as feeding intolerance.

Coordinated Sucking and Swallowing

From 12 to 16 weeks, the first signs of swallowing are seen in the fetus. It has been postulated that amniotic fluid (1) may play a role in providing luminal nutrients because it contains proteins, carbohydrates, and triglycerides; (2) provides volume, which stimulates the secretion of enteric hormone,
thereby promoting maturation of motility; and (3) contains large amounts of growth factors, which may play a role in the growth and differentiation of infant tissues. The fetus initially swallows small amounts of amniotic fluid (2 to 7 ml per day), and the volume increases with increasing gestational age. A fetus at term gestational age swallows approximately 300 to 700 ml per day. In animal studies, when saline was substituted for amniotic fluid, gut hypoplasia resulted.

Nutritive sucking and swallowing are not fully developed until approximately 34 weeks gestational age. Gestational age at birth and exposure to enteral feeds do not influence the development of the mechanism of nutritive sucking and swallowing. At 32 weeks gestation, upper esophageal sphincter function is detected. At this time, esophageal motility is not coordinated, and the motor activity is similar to that seen in older children with gastroesophageal reflux and dysmotility. Both increasing age and milk feedings promote maturity of esophageal motor activity.

Lower Esophageal Pressure

Acid reflux is prevented by a number of barrier mechanisms. The lower esophageal pressure is one such mechanism. In order to provide a barrier against reflux of stomach contents into the esophagus, the lower esophageal pressure must be higher than the fundal pressure. Studies have shown that at 26 weeks there is a high-pressure zone in the lower esophageal sphincter (LES). Sphincter pressure increases with gestational age. A 28-week gestational age infant has a less effective sphincter pressure (effective LES of 4 mmHg) than a term infant (effective LES of 18 mmHg). Maturation at the sphincter is not influenced by gestation at birth but is directly related to postconceptional age. The sphincter pressure rises with increasing postconceptional age. One can surmise that the lower esophageal pressure is a less effective antireflux barrier in a premature infant than in a term infant.

Gastric Emptying

Although swallowing is first observed at 12 to 16 weeks gestation, there is minimal evidence of transit through the gut before 30 weeks gestation. In adults, when milk enters the stomach, passive accommodation of the volume occurs as initially the antrum ceases to contract and duodenal contractions increase. Later, the antrum, pylorus, and duodenum contract in a coordinated fashion to empty the liquid in the stomach. Alteration in the function of coordination of motor activity in these areas can result in delayed gastric emptying.

The pattern of gastric emptying is different for liquids and for solids. Liquid meals empty in a curvilinear fashion, with rapid emptying that diminishes with time. The rate of liquid gastric emptying depends on the volume of the meal in the stomach. Gastric emptying of solid meals is controlled by the distal stomach, which prevents the passage of any particle greater than 2 mm. The pattern of gastric emptying of solid meals is predominantly linear.

Gastric emptying is slower in premature infants. The amplitude of the gastric antral contractions increases with increasing gestational age, with a fourfold increase noted between 28 and 38 weeks gestation (10 mmHg and 40 mmHg, respectively). Between 29 and 32 weeks gestation, both the number and amplitude of duodenal contractions increase markedly. In premature infants of 25 to 35 weeks gestation, antral activity was not always associated with duodenal activity. The association of antral activity with duodenal activity was five times lower in preterm infants than in term infants. With increasing gestational age, the percentage of antral activity with duodenal activity was significantly higher and appeared to be correlated with changes in duodenal motor activity. The lack of antroduodenal coordination in the preterm infants has been implicated in delayed gastric emptying. In addition, premature infants demonstrate poorly organized and nonrhythmic gastric pressure waves.

Dietary factors are known to affect gastric emptying. Gastric emptying is better with breast milk, glucose polymers, and medium-chain triglycerides. Gastric emptying is delayed with increasing energy density, higher fat, long-chain triglycerides and greater dextrose. Thus, altering milk composition may offer an avenue for promoting gastric emptying—and consequently feeding tolerance—for premature infants. Prokinetic agents that accelerate gastric emptying offer yet another avenue.

Intestinal Transit

Two types of intestinal motor pattern are observed in adults. The fed response is the first type of pattern; it is seen when food is ingested. At multiple levels of the intestine, there are simultaneous sporadic repetitive contractions of variable amplitude. These result in the mixing and churning of nutrients with gastric secretions. Nutrients are repeatedly presented to the mucosal surface as well. The second type of pattern is seen during fasting, when the intestine becomes relatively quiet and contractions disappear. This type of pattern consists of three consecutive phases. Phase I, referred to as the silent phase of motor quiescence, has no contractile activity. Phase II is marked by irregular contractions and is immediately followed by phase III, which consists of regular phasic contractions. The cycle repeats with phase I occurring after phase III; the three phases occur every 60 to 90 minutes. Phases II and III travel slowly down the intestine, and this behavioral pattern is called the migrating motor complex (MMC). The MMC is responsible for moving the nutrients forward; it has been called the “intestinal housekeeper.” Although the MMC appears between 32 and 35 weeks gestational age, it is poorly formed and shows disorganized, random bursts of motor activity. Furthermore, “the intervals
between complexes, amplitude of contractions, velocity of migration along the bowel, and reliability of propagation are less than in the adult.218

The MMC is under hormonal control. In adults, there is a sinusoidal cycle (a continuous waveform that is an equal distance above and below the baseline) of the hormone motilin. A concurrent increase in plasma motilin level is observed with the initiation of MMC. In premature infants, specifically those born at less than 32 weeks, there is no concurrent increase in plasma motilin level with the initiation of MMC. There is no modulation of MMC by motilin because two aspects of normal regulation of the MMC are absent in these infants. First, a functional antral smooth-muscle motilin receptor is not present until 32 weeks gestation. Second, there is no cyclic release of motilin.20 Cord blood has a low concentration of circulating motilin. Term infants,
on the other hand, show a higher concentration of circulating motilin in the cord blood.\textsuperscript{36}

The MMC is thought to be a marker for neuronal maturation of the small intestine. The MMC, however, is not essential for normal peristalsis. Dumont and Rudolph have demonstrated that newborn puppies are able to tolerate enteral feedings prior to the development of MMC.\textsuperscript{18} According to Berseth and Nordyke, feeding intolerance reflects a delay in the maturation of the neonate’s motor activity in the gut because these infants do not have complete interdigestive cycles during fasting. In addition, they are unable to change their pattern of motor activity in response to feedings.\textsuperscript{37}

Neuromuscular development of the gut begins early in gestation; however, normal patterns of contractile activity do not occur until after birth. Efficient sucking and swallowing develop at approximately 32 to 34 weeks gestation, and gastric emptying and intestinal propulsive activity mature after 30 weeks gestation (Table 2).\textsuperscript{18}

APPLICATION OF KNOWLEDGE TO CLINICAL PRACTICE

One could postulate that withholding enteral feedings after birth is unphysiologic.\textsuperscript{38} Nurses should ensure that minimal enteral nutrition is initiated soon after the birth of a premature infant. Minimal enteral nutrition—that is, “use of food not as a nutrient source but rather as a ‘medication’ to achieve biologic effects on the gut”—may play an important role in the nutritional management of infants born before 34 to 35 weeks gestation. Intraluminal stimuli—that is, enteral nutrition—promotes secretion of many gastrointestinal hormones, such as gastrin. According to Lucas, Bloom, and Aynsley-Green, infants who are fasting lack hormonal responses. Surges in plasma concentrations of gut hormones postnatally may be important in maintaining the drive to gut development.\textsuperscript{39}

Enteral nutrition may also be important in maintaining mucosal morphology and therefore the functional characteristics of the gastrointestinal tract.\textsuperscript{40} Atrophic changes in the gastrointestinal system, such as decreased weight of the intestine, pancreas, and stomach, are associated with withholding enteral feedings.\textsuperscript{41} Withholding feedings may have another adverse effect—that is, necrotizing enterocolitis (NEC). In 5 to 10 percent of cases, NEC occurs in babies who have never been fed.\textsuperscript{42,43} Studies examining the benefits of minimal enteral nutrition have lacked sufficient power to detect the negative outcome of NEC because of small sample sizes and the low incidence of NEC.\textsuperscript{44} Nurses should vigilantly assess for signs and symptoms of NEC in those babies who are receiving minimal enteral feedings.

Delayed gastric emptying in premature infants frequently presents as feeding intolerance\textsuperscript{45} resulting in abdominal distension, vomiting, and feeding residuals.\textsuperscript{46-47} Nurses should closely monitor infants for signs of feeding intolerance, document the type of feed being given, and observe relationships between type of feeding and feeding intolerance. Alteration in the composition of milk may offer an avenue for promoting gastric emptying, and consequently feeding tolerance, for premature infants.\textsuperscript{1}

Premature infants with feeding intolerance should not have feedings withheld; rather, an alternate strategy such as minimal enteral nutrition should be considered.\textsuperscript{18} Minimal enteral nutrition may be beneficial for those infants who exhibit an immature intestinal contractile activity because feeding promotes maturity of motor activity.\textsuperscript{18} The effect of minimal enteral feedings on gastrointestinal function has been examined in a number of studies.\textsuperscript{44-48} Minimal enteral feeders were reported to have improved feeding tolerance, decreased gastric residuals, fewer feeding interruptions,\textsuperscript{44,46} fewer days on total parenteral nutrition (TPN),\textsuperscript{44} and better weight gain by day 30 of life.\textsuperscript{49}

Prokinetic agents, such as cisapride, that accelerate gastric emptying may offer yet another avenue for the management of feeding intolerance.\textsuperscript{1} Lack of conclusive evidence from proper scientific methodologic trials, however, precludes clinicians from making any interpretation regarding the efficacy of cisapride in reducing the rate of feeding intolerance in premature infants.\textsuperscript{50} Premji and associates clarify the nurse’s role in assessing the relevant clinical outcomes of cisapride therapy.\textsuperscript{50}

In making a working clinical diagnosis of the causes of apnea and bradycardia in premature infants, reflux should be considered in the differential diagnosis. The timing of apnea and bradycardia (that is, during or soon after a feeding), and other clinical signs, such as tachypnea or abdominal distention, may provide clues to the possible etiology of reflux. Nurses should carefully observe the infant before, during, and after feedings and document apnea and bradycardia episodes and their relationship to feedings.

A review of the nursing literature verified that there are no randomized controlled trials on checking for feeding residuals or on the managing of feeding residuals. One small study showed that the practice of withdrawing feeding was not universal; however, 96 percent of neonatal nurses checked gastric residuals prior to each gavage feeding.\textsuperscript{51} The management of feeding residuals included, but was not limited to, refeeding at each feeding, refedding at most feedings, and never refedding. Rationale for the specific management strategy of refedding versus discarding the residuals included assessment of scientific evidence, the nurse’s personal assessment of potential harm or benefit to the infant, lack of institutional policy, and individual assessment of the type of residual (for example, whether it contained medication or milk versus mucus, bile, or old blood).\textsuperscript{51} Some authors suggest that gastric residuals contain gastric acid and enzymes that buffer the infant’s gastrointestinal system; it is known that they contain fluid and electrolytes. Consequently, if these residuals are discarded, electrolyte imbalance and metabolic complications may ensue.\textsuperscript{52-54} If nurses do discard feeding residuals, they must
monitor closely for signs and symptoms of electrolyte imbalance and metabolic complications.

Preterm infants do produce gastric acid. Bloody aspirates may suggest acid-peptic ulcers. Infants at high risk for acid-peptic mucosal damage may benefit from ranitidine (H₂ blocker) which increases gastric pH. Bloody aspirates should be promptly reported to medical staff so that the infant can be assessed for acid-peptic disease.

CONCLUSION

By approximately 34 to 35 weeks gestational age, the gastrointestinal system is capable of effective digestion of enteral nutrients. Consequently, infants born at 34 to 35 weeks gestation have intact neuromuscular function and the structurally and functionally mature foregut needed to tolerate enteral feedings without medical intervention. The nutritional management of infants born before 34 to 35 weeks gestation requires an awareness of gastrointestinal ontogeny, particularly the effects of the intrauterine and extraterrine environments upon that process. Decisions related to feeding premature infants should also be based upon current research.

REFERENCES


About the Author
Shahroz S. Premji is currently employed as a clinical nurse specialist-neonatal practitioner at the Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario, Canada. She is a part-time doctoral student in the Clinical Health Sciences (Nursing) Program at McMaster University. She received a bachelor of science in nursing degree and neonatal practitioner certificate from McMaster University and a master of science (nursing) degree from the University of Toronto.

The author wishes to thank Dr. Janet Pinelli for her academic, professional, personal, and editorial support. Thanks to B. Faed, MD, FRCP(C), and K. Jacobson, MBBCh, FRCP(C), for their invaluable expertise and guidance in the writing of this manuscript. Also, thanks to Jennifer Wilson, CNS-NP, for her friendship and editorial support.

For further information, please contact:
Shahroz S. Premji, RN, MSc(N)
Clinical Nurse Specialist-Neonatal Practitioner
Hamilton Health Sciences Corporation, McMaster Site
Neonatal Unit—4G
Children’s Hospital
1200 Main Street West
Hamilton, Ontario, Canada L8N 3Z5
e-mail: Premji@hhs.cmh.on.ca

Correction
Due to printer error, the table on pages 20 and 21 of the article “Heelsticks in Neonates for Capillary Blood Sampling” that appeared in the February 1998 (Vol. 17, No. 1) issue of Neonatal Network® was printed incorrectly. We apologize to the author and readers for this error and would like to reprint it correctly. Unfortunately, it was too late for this issue; but look for the corrected table in the April 1998 issue of Neonatal Network®.
Appendix B-2

January 18, 2000

Tom English
Editorial Assistant
Stockton Press
345 Park Avenue South, 10th Floor
New York NY100010-1707 USA

Dear Mr. English:

I am completing a Ph.D. thesis at McMaster University entitled "Feeding Practice Guidelines for Premature Infants Less Than 1500 Grams: Efficacy and Safety". I would like to request permission to reprint the proofs of the article entitled "Gastrointestinal function and growth in premature infants: Is non-nutritive sucking vital?" in my thesis. The article has been accepted for publication in the Journal of Perinatology.

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Sincerely,

[Signature]

Shahroose S. Premji, Ph.D.(c)
Clinical Nurse-Specialist/Neonatal Practitioner
Hamilton Health Sciences Corporation
Children’s Hospital Neonatal Unit - MUMC 4G
1200 Main St. West
Hamilton, Ontario
L8N 3Z5
Phone: (905) 521-5025
Fax: (905) 521-5007
E-mail: premji@hhsc.ca
Gastrointestinal Function and Growth in Premature Infants: Is Non-Nutritive Sucking Vital?

Shahrirose S. Premji, PhD (candidate)
B. Paes, MD, FRCP(I), FRCP(C)

OBJECTIVE:
To determine the importance of non-nutritive sucking (NNS) in the growth of premature infants at 24 weeks of gestation.

DATA SOURCES:
1. Medical records of premature infants at 24 weeks of gestation at the University of Toronto, Toronto, Canada.
2. Literature review of NNS in premature infants.

STUDY SELECTION:
Premature infants at 24 weeks of gestation were selected for study.

DATA EXTRACTION:
Data were collected on NNS, growth parameters, and feeding patterns.

DATA SYNTHESIS:
NNS was found to be significantly correlated with growth parameters.

The sucking response is characteristic of intrauterine fetal life and early infancy but becomes rapidly insignificant by the end of the first year. Effective sucking behavior is a prerequisite for safe and effective oral feeding and implies that an infant has achieved neurologic, behavioral, and physiological maturity. Sucking behaviors have been classified into two modes, namely nutritive and non-nutritive sucking (NNS), based on sucking patterns. Nutritive sucking has a continuous rhythmic pattern that consists of slower mean rates of sucking, usually about half that of NNS, with shorter periods of pauses. Nutritive sucking occurs solely in the presence of oral fluid. NNS alternates between unpredictable bursts of activity and rest periods in the absence of oral fluid intake such as amniotic fluid or milk and is characterized by a rapid rate of sucking (approximately two or more sucks per second).

Premature infants, especially those of very low birth weight, encounter unique problems during their postnatal course, such as respiratory distress syndrome, apnea, and patent ductus arteriosus. These problems frequently complicate their clinical course and nutritional management, resulting in increased morbidity and longer hospitalization. When medically stable, premature infants are gavage fed because the nutritive sucking and swallowing mechanism is not fully developed until —32 to 34 weeks' gestation. Not only are sucking opportunities limited for these fragile infants, but exposure to NNS is rarely provided during tube feedings. Offering premature infants the experience of NNS during tube feedings may afford the necessary stimulus for the normal development of sucking behaviors, specifically, a mature NNS response.

A major obstacle to successful feeding of premature infants relates to the functional immaturity of the gastrointestinal system. Gastric emptying matures after 30 weeks' gestation. Delayed gastric emptying frequently presents as feeding intolerance, which clinically manifests in abdominal distention, vomiting, and feeding residuals. Premature infants who are intolerant of feeds are maintained on parenteral nutrition, which limits the provision of calories necessary for maximizing weight gain. As a result, these infants take longer to establish full feeds and to achieve early discharge from the hospital. A physiologically supportive intervention that facilitates maturation of the gastrointestinal system and promotes weight gain and earlier hospital discharge would be desirable. In premature infants, a pacifier provides opportunities for NNS and may be viewed as physiologically supportive.

The primary objective of this review is to determine the importance of NNS in the development of gastrointestinal function and growth in premature infants. The critical outcomes examined include gastric emptying, weight gain, and time to discharge from hospital. The secondary objective is to assess the impact of pacifiers on the
development of sucking behaviors, specifically, the sucking response. The critique synthesizes the existing body of NNS research to describe how results vary across studies. Limitations in the existing research are examined, and potential clinical research in the area of NNS is identified.

Assessing the effects of NNS first requires an understanding of the development of NNS in premature infants; related factors, including gestational age, postnatal age, and health status; and the proposed mechanisms of action.

DEVELOPMENT OF NNS AND RELATED FACTORS

NNS develops before nutritive sucking, and in its immature form consists of only mouthing movements. Although NNS is evident at approximately 24 weeks, the rate of NNS is slower, the number of suck in each burst is smaller, and the sucking pressure is lower. The NNS pattern is not mature until 37 weeks' gestation. The sucking pattern undergoes a quantitative change with increasing postnatal age. There is decreased variability of the sucking pattern (burst/pause rhythm) and the initial short bursts of sucking become longer and the frequency of sucking is reduced. Infants who are offered a pacifier retain the ability to suck in the non-nutritive mode up to 4 years of age. Altering the shape of the nipple does not affect the temporal organization of NNS. In the course of time, NNS is not retained as a significant activity. Infants stop NNS either because of loss of ability or willingness. NNS, however, does not disappear from the infant's repertoire, but rather, may reappear in later adult life with severe central nervous system (CNS) diseases such as senility.

The development of NNS is affected by the presence of cerebroventricular hemorrhage and ventricular dilation. According to Wolf, any disorder that affects the CNS will inadvertently disturb the temporal organization of NNS. It has been postulated that even minor disturbances of CNS function such as perinatal distress, without any obvious neurologic impairment, may alter the NNS response. NNS is thought to be more resistant to perinatal risk factors than nutritive sucking. Illness also alters the characteristics of NNS. The quality of the suck varies inversely with the infant's respiratory status. An abnormal NNS response, however, is not predictive of later neurologic or behavioral outcome.

Behavioral states influence the rhythmical organization of NNS. Parameters such as the mean frequency per burst per second, length of bursts and rest periods, and amplitude of suck may change significantly from one state to another. Wolf states that NNS "may be difficult to elicit during any kind of sleep for the first half hour after a feeding." Variability is greatest during sleep and waking states than in regular sleep. Within one state there is marked individual but little intra-individual variation. However, the total amount of sucking is not related to levels of excitation; hence, state has only a minor influence on the overall organization of NNS.

Paradoxically, NNS significantly affects behavioral state. Preterm infants who were given a pacifier during and after feeding were less distressed. These infants spent less time in fussy and active awake states and more time in inactive and awake behavioral states. There were fewer changes in behavioral states during feedings; quiet, awake states were more frequent. In addition, these infants returned to a sleep state much faster.

One mechanism that has been postulated for the potential beneficial effect of NNS, that of improved weight gain, has been attributed to the optimal behavior states achieved with NNS. General movements of the limbs, head, and trunk occur without a distinctive pattern or sequencing of the various body parts. These general movements are endogenous in nature. The forms of general movement differ in different behavioral states and are absent during quiet wakefulness. NNS alters behavioral state such that infants are in optimal quiet states, thereby decreasing general movements and conserving energy. The reduced energy expenditure may contribute to weight gain.

A second mechanism in support of improved weight gain and enhanced gastrointestinal function is thought to be related to the effect of NNS on enzymes and hormones. NNS is postulated to stimulate tissues in and around the base of the tongue, resulting in secretion of an enzyme called pharyngeal lipase. Pharyngeal lipase improves fat digestion, and it may be that the reduced energy expenditure in the process facilitates weight gain. However, the practical significance of pharyngeal lipase in preterm infants has yet to be determined, and as studies have found no differences in energy expenditure between treated (NNS) and control groups. In addition, one study found no difference in lipase activity between cohorts of premature infants receiving gavage feeding exclusively and gavage feeding with NNS.

NNS is also thought to stimulate fibers in the oral cavity that activate the vagal nerve. Activation of the vagal nerve influences the levels of gastrointestinal hormones such as gastrin and somatostatin. Secretion of gastrin is necessary for acid secretion, gastric motility, and intestinal mucosa growth. A decrease in somatostatin hormone promotes gastric emptying. Regulation of gastrointestinal hormones leads to stimulation of gastrointestinal motor and sensory activity, growth of the intestinal tract, and enhanced release of glucose-induced insulin. Increased insulin production promotes glucose utilization. Consequently, vagal activation by NNS may lead to enhanced mixing, propulsion, optimal digestion and absorption of nutrients, and expulsion of waste products.

Marchini et al. found that preterm infants provided with NNS had a significant increase in insulin levels; however, these findings were not supported by Kanarek and Shulman. Widstrom et al. found decreased somatostatin and increased gastrin levels in gastric aspirates of preterm infants that were allowed to suck on a pacifier during gavage feedings. Other studies have found that gastrin and somatostatin levels were not significantly altered in treatment and control groups.

Although the specific mechanism(s) of the effects of NNS has not been established, the provision of NNS during tube feedings may have beneficial outcomes that are of particular importance to premature infants.
CRITICAL ASSESSMENT OF EXISTING NNS RESEARCH

A systematic, computerized search of MEDLINE, the Cumulative Index of Nursing in Allied Health Literature, Health, Best Evidence, and the Cochrane Library was performed to identify publications that focused on the use of pacifiers or NNS as well as on the importance of NNS in the development of gastrointestinal function and infant growth. Medical subject headings used included NNS; sucking behavior; pacifiers; feeding behavior; infant nutrition; enteral nutrition; gastric emptying; growth; weight gain; infant, premature; and infant, newborn. For the purpose of this review, the findings of all prospective, methodological studies have been summarized in relation to the outcomes of interest (see Table 1). The critical appraisal of these studies is based on an assessment of variables that may affect the outcomes of interest.

CRITICAL APPRAISAL OF STUDIES AND FINDINGS

Randomized Controlled Trials

Randomized controlled trials are the most powerful design available to evaluate the efficacy of a clinical intervention such as NNS. In practice, the random allocation of subjects to the defined intervention, NNS, allows the researcher to equally balance the distribution of both known prognostic factors (e.g., gestation age and postnatal age) and unknown determinants that may threaten the validity of the results. "Blinding" of the intervention, such as NNS during gavage feeding, from the researcher is also of paramount importance to avoid distortion and bias in the assessment of outcome measures. In deciding whether NNS is beneficial to all infants exposed to this strategy, it is necessary to methodologically appraise the existing body of evidence using sound scientific criteria. To date, eight randomized controlled trials have been published (see Table 1).

Factors Influencing the Outcomes of Interest

Three of the randomized controlled trials are crossover studies in which the effects of NNS are examined in a single group. Practically, these studies are relatively easy, less expensive, and can be conducted over shorter periods of time. The subjects serve as their own controls; therefore, personal factors such as gestational age and birth weight are the same; consequently, these factors do not influence the outcome of interest. However, age-related changes are not controlled for, and, as a result, cause and effect is difficult to establish.

As discussed previously, perinatal distress may potentially alter the NNS response. Apparent scores (<3 and 5 at 1 minute and 5 minutes, respectively) and/or signs of perinatal distress such as seizures/asphyxia were used to exclude babies from selective studies. Field et al. used a tool, the obstetric complication scale, to assess the obstetric factors affecting study infants. The reliability and validity of this scale, however, is uncertain.

The health state of the infant can also affect the characteristics of NNS. Field et al. used a postnatal complication scale that included conditions that reflected an increased risk of mortality and morbidity (e.g., respiratory distress syndrome and metabolic and temperature disturbances) to assess characteristics of infants in the treatment and control groups. No statistically significant differences were present between groups with the use of this scale. The appropriateness of such a scale is questionable, because it was developed in 1978 and did not include conditions such as necrotizing enterocolitis and patent ductus arteriosus. These conditions can be major complications of prematurity. To overcome the limitations of the scale, the prevalence of necrotizing enterocolitis was identified, and there was no significant difference between control and treatment groups.

The development of NNS is also affected by the presence of intraventricular hemorrhage and ventricular dilatation. Mattes et al. excluded infants with grade 3 or 4 intraventricular hemorrhages documented on ultrasound, and Bernbaum et al. excluded infants based on clinical evidence of intraventricular hemorrhage. The absence of ultrasonographic confirmation of intraventricular hemorrhage in the latter study makes the reliability and validity of the data questionable. Infants with seizures or signs of hypoxic ischemic encephalopathy were excluded in both studies, because any disorder that affects the CNS will inadvertently disturb the temporal organization of NNS.

Tactile stimulation (e.g., touch) will also result in the release of vagally regulated hormones and, as a result, promote weight gain through a similar mechanism to NNS. Although Bernbaum et al. controlled for such environmental factors by maintaining infants in the incubator during feeding, it is uncertain how much tactile stimulation the infants received during feedings.

Selection of Subjects

Sampling is a critical factor, as it determines how accurately the targeted population is represented. Selection of subjects is one area that investigators must consider when examining sampling. A random selection process was used by some researchers (e.g., random stratified by Field et al.) to ensure that each subject in the target population had an independent chance of being included in the study and was also exposed to predetermined factors that might have influenced outcome. Despite attempts to ensure that a representative sample was selected from the targeted population, in the study by Field et al., the sample was skewed toward male sex.

A predetermined sample size is critical, as it permits the researchers to achieve both clinical and statistical significance in a study and to make generalizations regarding their findings on similar populations of infants. It appears that convenience sampling was used in all trials, as the researchers do not present power analyses or justify the appropriateness of the number of subjects used. Convenience sampling is usually used in pilot studies to determine the effect of a treatment strategy before launching a large-scale controlled trial. Such studies with a similarly defined hypothesis and identical outcome measures can also be used cumulatively in a meta-analysis to improve the power of a study.

Treatment

Duration of treatment was variable across studies. Consequently, the studies limit the reader's understanding of the effect of NNS on the
Table 1. Randomized Controlled Trials: Characteristics, Outcomes, and Appraisals.

<table>
<thead>
<tr>
<th>Study, investigator</th>
<th>Design</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Seeking sequence</th>
<th>Genetic mapping</th>
<th>Weight gain</th>
<th>Time to discharge</th>
<th>Appraisal (strength and limitations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mead and Ackerman</td>
<td>Alternate sequential series E = 20</td>
<td>C = 30</td>
<td>28-34 weeks &gt;1500 gm</td>
<td>During and 3 minutes after every feeding to tolerate full feed and solids; begin with first food group after 30% of inclusion</td>
<td>E = 2.6 gm more per day; NS earlier, p &lt; 0.05</td>
<td>Sample of stable protein intake; duration of study 6 to 12 months; control for calciferol intake; pediatric use at other times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Field et al</td>
<td>Randomized for GA and BW GA and BW C = 27</td>
<td>&gt;35 weeks (mean 35)</td>
<td>During every tube feeding; begin with first food group after 30% of inclusion</td>
<td>C = nocturnal process score on NASIC</td>
<td>E = 2.8 gm more per day, NS earlier, p &lt; 0.05</td>
<td>Ccalcium intake not controlled; pediatric use at other times; sodium intake to mean 2000 mg, caloric intake to 1000 kcal; subjects were all male; NASIC at 1 month postdischarge E = C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randerson et al</td>
<td>Pair randomly assigned C = 19</td>
<td>E = 20</td>
<td>52 weeks &gt;1500 gm</td>
<td>During every tube feeding; begin with first food group after 30% of inclusion</td>
<td>E = increased looking efficiency P &lt; 0.05</td>
<td>E = 213 gm more per week; NS difference significantly; 2 weeks P &lt; 0.02</td>
<td>Subjective evaluation of FS: No significant difference; no differences in feeding opportunities in C group; in E group; no significant difference in feeding control for calciferol intake</td>
<td></td>
</tr>
<tr>
<td>Ernst et al</td>
<td>Randomly assigned by sex and BW C = 9</td>
<td>E = 9</td>
<td>&lt;30 weeks &lt;1500 gm</td>
<td>During each feeding 12 times per day for 30 minutes until reached 1000 gm, then 8 times per day</td>
<td>NS difference</td>
<td>Duration of FS was 12 weeks; no significant differences in feeding patterns between groups; no differences in food intake; no differences in feeding opportunities in both groups; no differences in energy intake amongst groups; small sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mann et al</td>
<td>Randomly assigned</td>
<td>Sweet pacifier, N = 54 weeks</td>
<td>&lt;1500 gm</td>
<td>Sweetened edible pacifier during all feeding periods until able to tolerate full feed and solids; sweetened edible pacifier substituted for baby pacifier; played a tape recording of maternal heart sound to mean of non-nutritive stimulation</td>
<td>NS difference among treatment groups</td>
<td>NS difference among treatment groups (scored the sweet pacifier group)</td>
<td>No difference in energy intake among study groups; no differences in the amount of feed allowed at 24 hours; no differences in total caloric intake at start of study 15% decrease in feeding efficiency; decrease number of infants at each week of study and point at which final feeding level is reached; analysis performed at least 2 weeks (mean 8) and 10 weeks</td>
<td></td>
</tr>
<tr>
<td>Seals et al</td>
<td>Crossover randomly assigned before study</td>
<td>N = 10</td>
<td>52-56 weeks (mean 54) &gt;1500 gm</td>
<td>Seck on pacifier for 5 minutes while food administration; test feed allowed to drip by gravity over 1-5 minutes (approximately 2-70 hours for crossover effect)</td>
<td>NS difference at 10, 20, and 30 minutes;</td>
<td>NS difference at 10, 20, and 30 minutes;</td>
<td>Small sample size; no difference in energy and nitrogen balance, net nitrogen utilization, or fat absorption</td>
<td></td>
</tr>
<tr>
<td>Derusso et al</td>
<td>Crossover randomly allocated to study</td>
<td>N = 10</td>
<td>Mean GA, 283 + 5 days during which infant studied on pacifier for the duration of feeding (mean 10) to 15 2 days for crossover effect</td>
<td>NS difference in energy and nitrogen balance, net nitrogen utilization, or fat absorption</td>
<td></td>
<td></td>
<td>Small sample size, no difference in energy and nitrogen balance, net nitrogen utilization, or fat absorption</td>
<td></td>
</tr>
<tr>
<td>Widdowson et al</td>
<td>Crossover randomly assigned</td>
<td>N = 8</td>
<td>Mean BW, 11256 gm, mean GA, 52.3 weeks</td>
<td>Pacifier 15 minutes before and during each tube feeding, access to pacifier 3 hours following feeding; Two experiments on two consecutive days</td>
<td>NS difference in gastric residual volume</td>
<td>Small sample size; able to take 3 to 4 feeds/day by bottle given same amount of milk in two experiments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**a.** number; **b.** experimental; **c.** control; **NS.** non-significant; **DC.** discharge; **GA.** gestational age; **BW.** birth weight; **GA.** treatment.

*This power calculation for sample size.*
outcomes of interest, because the studies cannot be compared. In addition, no inferences can be made about the relationship between NNS and the outcomes of interest. The duration of NNS during feedings or vagal stimulation varied from 5 to 30 minutes. Ernst et al. 6 offered infants a pacifier for 30 minutes with each feeding every 2 hours. There was no significant difference in weight gain between the treatment and control groups in this study. In some studies, it is unclear how much time infants in each group spent suckling on a pacifier, as infants in both control and treatment groups were also exposed to the same intervention between feedings. 35 These studies showed significant differences in weight gain between treatment and control groups.

All crossover studies 25-27 allowed for a lag time between treatment and no treatment. Although this is important to avoid contamination from the effects of the initial strategy, it is uncertain whether such an approach minimizes the effects of age, weight, and maturation differences. In addition, it is unclear how much time is adequate for “washout” so that there is no “crossover” effect. Two studies had short periods of intervention (one feed), which may not be sufficient to affect the outcomes of interest. 25-27 Bernbaum et al. 25 found that differences in outcomes such as weight gain were not evident until the second week of the study.

Outcomes of All Studies

NNS and sucking response. Three studies attempted to determine the benefit of pacifier use as a physiologically supportive intervention 25-27 in the maturation of a sucking response. Studies either examined the sucking pattern 25 or assessed later bottle feeding behavior and performance by the Brazelton Neonatal Behavior Assessment Scale. 25

Field et al. 25 found no significant difference in feeding performance between treatment and control infants. The parameters used to assess feeding performance included incidence of regurgitation, volume of formula intake, and length of feeding time. In addition, “an objective, time-sampling procedure used to record infant and nurse behaviors...suggest[ed] that the control infants required more ‘ coaxing to feed.’” 25 The time-sampling procedure was not described. Mates et al. 26 also found no differences in sucking performance as measured by frequency (i.e., number of sucks per minute) and strength of suck.

Bernbaum et al. 25 found that the infants in the NNS group developed a more organized pattern of sucking with increasing age as evident from the greater number of sucks per burst and fewer sporadic sucks (10.5 ± 2.0 vs 8.0 ± 1.5, p < 0.05). In addition, the organization and efficiency of the sucking pattern was accelerated in these infants, evident as early as 34 weeks after conception, and the differences remained significant until discharge. Field et al. 25 point out that the benefits of NNS need to be interpreted with some discretion, as the evaluative performance of premature infants on the Brazelton Neonatal Behavior Assessment Scale was not optimal. The treated infants showed weak reflexes more frequently as evidenced on the motoric cluster score of the Brazelton Neonatal Behavior Assessment Scale (p = 0.06). A subsample of their study infants showed no difference on the motoric cluster score of the Brazelton Neonatal Behavior Assessment Scale at 1 month after discharge. Although the differences disappear in time, the impact of periodic stressors on the CNS remains questionable.

Gastric emptying. Two crossover studies evaluated the effect of a pacifier on gastric emptying. 25-27 Both studies showed no significant difference in gastric emptying between treated and control groups. The small sample size may have precluded the researchers from finding statistically significant differences. In addition, both studies had short periods of intervention (one feed), which may not be sufficient to evaluate gastric emptying. Widstrom et al. 26 recorded the volume of gastric contents, a measure of gastric emptying, 3 hours after bolus feeding in both groups. The volume of milk was based on the age and weight of the infant. The infant was given the same type of milk (banked pasteurized human milk or fresh own mother’s milk) for the two experiments. The study showed decreased gastric retention with the use of a pacifier. The difference, however, was not statistically significant. Gastric retention was also measured in the study by Szabo et al. 27 Phenol red marker was used to determine gastric emptying at 10, 20, and 30 minutes after the test meal, which consisted of 10% dextrose. Three feeding methods were evaluated in each infant: NNS, nutritive suck, and control. NNS did not significantly improve gastric emptying. Gastric emptying is affected by dietary factors and is faster with human milk. 41 Gastric emptying is delayed with increasing energy density, 41 higher fat, 41 and greater dextrose concentration. 41 Thus, these two crossover studies cannot be compared, because the composition of the “feed” differs.

Enteral nutrition stimulates the secretion of many gastrointestinal hormones, such as gastrin. According to Lucass et al., 26 infants who are fasting lack hormonal responses that may be important in maintaining the drive for gut development. In addition, enteral nutrition is important in maintaining mucosal morphology, and therefore, the functional characteristics of the gastrointestinal tract. 42,43 Feeding promotes maturity of motor activity; therefore, it is important to consider timing of feeds when assessing the effects of an intervention on gastric emptying. Both studies failed to examine the timing of feeds in their sample of premature infants.

Weight gain. A number of studies have reported improved weight gain in premature infants who were encouraged to suck on a pacifier during gavage feedings. 25-27 Field et al. 25 failed to report the energy intakes in the two groups. When energy intake was controlled, preterm neonates offered NNS during gavage feedings had significantly more rapid weight gain. 25 These studies, however, do not report the nutritional status of the infants at entry into the study. In contrast, other studies have reported that NNS had no effect on weight gain. 44,45 Ernst et al. 44 took precautions to equalize nutrient intake in the two study groups, and NNS had no effect on weight gain over a 14-day period of gavage feeding. The weight gain observed in the NNS group was attributed to enhanced nutrient absorption. Results of a study conducted by DeCurtis et al. 45 showed no significant difference in
nutrient absorption between treated and control groups. However, their study was conducted over a short period (3 days); hence, the study neither confirms nor refutes the positive effect of weight gain resulting from NNS. Bernbaum et al.\textsuperscript{5} observed that weight gain differences were not apparent until the second week of the study period.

**Time to discharge from hospital.** Three studies\textsuperscript{5,35} found that the time to discharge from hospital was shorter in NNS groups. Two studies\textsuperscript{35} used weight, 2 kg and 1.8 kg, respectively, as a measure of readiness for discharge. In the study by Meisel and Anderson,\textsuperscript{7} the infant's physician determined when the infant would be discharged. The researchers had no input into this decision, thereby eliminating bias. Field et al.\textsuperscript{35} found significant group differences in hospital cost, with the treated infants having a lower hospital cost than control infants.

**Summary of the Limitations**

The current scientific literature in the field of NNS yields conflicting results. Some studies indicate NNS to be a physiologically supportive intervention facilitating gastric emptying,\textsuperscript{28} promoting weight gain, and earlier discharge;\textsuperscript{5,35} whereas others show no conclusive evidence in favor of NNS.\textsuperscript{62,64,65} The studies reviewed are difficult to interpret for a number of reasons. From this discussion it is evident that this stems primarily from the lack of large-scale controlled trials and studies that have varied objectives and outcomes. Both known and unknown variables that may significantly affect the outcomes were not consistently controlled because of the absence of randomization, stratification, and rigid inclusion/exclusion criteria. The NNS intervention varied in timing and duration over the study period, and in the majority of studies the absence of "blinding" of the investigators could potentially distort the results. The research methodology was not robust because of small sample sizes, weak study design (e.g., crossover studies), and measurement tools that were not valid or reliable. Finally, these studies focused primarily on stable cohorts of premature infants (non-ventilated), thereby limiting the findings to this particular demographic population.

**Meta-Analysis of NNS**

As mentioned previously, randomized controlled trials can be used cumulatively in a meta-analysis to improve the power of a study, thereby enabling the clinician to draw more definitive conclusions. There are three published meta-analyses of NNS.\textsuperscript{46-48} These involve comprehensive literature searches of published and unpublished randomized trials and systematic reviews with clearly defined outcomes. However, the studies included in the meta-analyses varied, based on stringent selection criteria. Steer et al.\textsuperscript{49} showed a statistically significant increase in weight gain of 2.2 gm per day (95% confidence interval: 0.6, 3.8), which was thought to be clinically insignificant. The other two meta-analyses\textsuperscript{48,49} demonstrated no clear benefit of NNS on weight gain. Based on these meta-analyses, the effect of NNS on weight gain remains inconclusive.

The length of hospitalization was uniformly decreased in all three meta-analyses. The weighted mean difference was — 5.9 days (95% confidence interval: — 10.0, — 1.7) and — 7.14 days (95% confidence interval: — 12.59, — 1.69) in the reviews by Steer et al.\textsuperscript{49} and Pinelli and Symington,\textsuperscript{48} respectively. Schwartz et al.\textsuperscript{48} do not report weighted mean difference but determined that preterm infants in the NNS group were discharged 4 to 8 days earlier. Although hospital costs were not systematically evaluated in the three meta-analyses, it seems reasonable to conclude that the observed decrease in the duration of hospitalization would result in savings to neonatal units.

**IMPLICATIONS FOR FUTURE RESEARCH**

Although universal recommendations regarding the use of NNS cannot be made based on the randomized controlled trials and meta-analyses, the literature review clearly indicates a decrease in the length of hospitalization for preterm infants without any negative outcomes. However, the implications for clinical practice elicit many questions. One can postulate that although NNS is dependent primarily on physiological maturation, experience may strengthen or change the development of sucking activity to enhance nutrition and subsequent growth. The development of other reflexes (e.g., cough reflex), however, are necessary for effective and safe oral feedings.

Which population of infants is most receptive to NNS? Is there a dose response relationship? Are the growth curves of infants exposed to NNS superior to those of control infants? What effect(s) does NNS have on the neurodevelopment of premature infants? Will these experiences lead to long-term differences in behavior (e.g., aversive oral behavior) or learning abilities? A better understanding of the mechanism(s) involved in NNS will help to critically assess the benefits or adverse effects of NNS. There are many avenues for further research.

To accurately assess the effects of NNS on sucking response, gastric emptying, and weight gain, a randomized, stratified controlled trial of sufficient power is recommended. Strata may be determined based on gestational age, obstetrical status, and health risk status. Each factor should be accounted for at study entry by matching, standardization, careful selection criteria, or stratification based on major confounding variables. Instruments used to measure obstetrical and health risk status must be reliable, tested, and valid. Data from previous studies could be used to calculate an appropriate sample size a priori. The NNS intervention (duration and context) should be clearly described and begin with the first feed, continuing until the infants reach full enteral feeds without contamination of the control cohort of infants. Data collection should include variables that potentially impact on the outcomes of interest. Care procedures such as intubation (oral versus nasal) for ventilation, oral versus nasal gavage tubes, handling, and delayed oral intake should be documented. Finally, to confidently evaluate the effects of NNS, long-term outcomes such as growth and neurodevelopment should be assessed in an unbiased, blinded, management trial.

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34. Guyatt GH, Sackett DL, Cook DJ. User’s guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994;271:59–63.


Appendix B-3

January 18, 2000

Judyann Silbo
Permissions Coordinator
Neonatal Network

Dear Ms. Silbo:

I am completing a Ph.D. thesis at McMaster University entitled “Feeding Practice Guidelines for Premature Infants Less Than 1500 Grams: Efficacy and Safety”. I would like to request permission to reprint the following articles in my thesis. Additionally, I would like permission to reprint or adopt tables for this thesis. I am the sole or principal author of these articles.


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I would appreciate it a great deal if you would send me written permission (by mail and/or fax) to reprint these articles in my thesis. Thank you very much for your assistance in this matter.

Sincerely,

[Signature]

Shabirose S. Premji, Ph.D.(c)
Clinical Nurse Specialist/Neonatal Practitioner
Hamilton Health Sciences Corporation
Children’s Hospital Neonatal Unit - MUMC 4G
1200 Main St. West
Hamilton, Ontario
L8N 3Z5
Phone: (905) 521-5025
Fax: (905) 521-5007
E-mail: premj@hhsc.ca
Cisapride: A Review of the Evidence Supporting Its Use in Premature Infants with Feeding Intolerance

Shahirose S. Premji, MSc(N)
Jennifer Wilson, MHSc
Bosco Paes, FRCP(I), FRCP(C)
Shari Gray, BScPhm

The incidence of feeding intolerance was 67 percent in infants weighing less than 1,500 gm, according to a retrospective chart audit conducted in a 34-bed NICU in a university-affiliated teaching hospital. Considering the improved survival rates for small premature infants—especially those who are born weighing less than 1,500 gm—over the past two to three decades, the magnitude of the problem of feeding intolerance can be appreciated. Ohlson and colleagues, for example, report that for neonates with a birth weight of 500–750 gm, survival rates reach 65 percent.

Providing nutritional support to this increasing number of small preterm infant survivors is a major challenge. The goals of nutrition for these small preterm infants are not universally accepted and are frequently revised to optimize growth and neurodevelopmental outcome. Many neonatologists, however, propose that one goal may be to prevent feeding-related morbidities such as feeding intolerance, which results in abdominal distension, vomiting, and feeding residuals.

GASTRIC MOTILITY IN PREMATURE INFANTS

In general, during fasting, intestinal motor activity has a cyclic pattern lasting approximately 90 minutes. Very little activity occurs during the first part of this cycle. In contrast, during the end of the cycle, according to Bisset and associates, "a highly organized propagated band of activity called the migrating motor complex passes from the stomach to the ileum." The migrating motor complex is believed to coordinate the movement of milk through the intestine. Intestinal motor activity increases in magnitude and organization with increasing gestational age—that is, motor activity matures with increasing gestational age. Enteral nutrition also promotes maturity of the motor activity.

Differences in gastrointestinal motor activity have been documented between infants who tolerate feeds and those who experience feeding intolerance. According to Berseth and Nundyke, feeding intolerance reflects a delay in the maturation of the neonate's motor

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activity in the gut. Infants with feeding intolerance do not have complete interdigestive cycles during fasting, nor are they able to change their pattern of motor activity in response to feeds. The inability of these infants to initiate the “fed response” was evident in the differences in manometry recording during fasting, which was characterized by “more clustered motor activity [and] less quiescence.” Although this pattern of intestinal activity was transient, it took four weeks to resolve. Consequently, it takes longer to establish feeding intolerant babies on full oral feeds and discharge them from the hospital.

During this transient time period when the pattern of intestinal activity in infants with feeding intolerance is resolving, these small preterm infants are kept on parenteral nutrition. Parenteral nutrition, however, does not promote maturity of intestinal motor activity, so it does not enhance maturation of the preterm infant’s small intestine. Furthermore, many adverse effects, including cholestasis jaundice, have been associated with prolonged use of parenteral nutrition.

**CISAPRIDE PHARMACOLOGY**

Cisapride is thought to specifically enhance the physiologic release of acetylcholine at the myenteric plexus of the intestine. The stimulatory effect of the drug on gastrointestinal motility mimics the natural progression of maturation of the migrating motor complex. Gastric emptying is accelerated by an increase in gastric and duodenal contractility. Gastric reflux into the esophagus is decreased through a mechanism of increasing esophageal peristaltic activity and enhancing esophageal

**TABLE 1** Summary of Search Routes for Literature Review on Use of Cisapride for Feeding Intolerance in Premature Infants

<table>
<thead>
<tr>
<th>Search Route</th>
<th>Year Published</th>
<th>Total Number of Citations</th>
<th>Relevant References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>12</td>
<td>8</td>
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<tr>
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<td>0</td>
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</tbody>
</table>

*Same articles

**TABLE 2** Summary of the Three Clinical Trials on Use of Cisapride for Feeding Intolerance in Premature Infants

<table>
<thead>
<tr>
<th>References</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Gestational Age (Range)</th>
<th>Weight (Mean)</th>
<th>Age at Enrollment (Mean)</th>
<th>Dose</th>
<th>Duration (Mean)</th>
<th>Feeding Mode</th>
<th>Type of Feeding</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melis, Janssens (1990)</td>
<td>Open case series</td>
<td>20</td>
<td>26–34 [30.5]</td>
<td>780–2,330 [1,485]</td>
<td>2–55 [18]</td>
<td>0.15 mg/kg QID, 30 minutes prefeed</td>
<td>6–171 [38]</td>
<td>Continuous</td>
<td>Formula</td>
<td>Decreased gastric residuals (p &lt;.0001) Increased feed volume in last 24 hours of cisapride treatment (p &lt;.001)</td>
</tr>
<tr>
<td>Janssens (1987)</td>
<td>Open case series</td>
<td>14</td>
<td>29–38 [32]</td>
<td>800–2,070 [1,595]</td>
<td>1–57 [17]</td>
<td>0.16 mg/kg QID, prefeed</td>
<td>5–55 [18]</td>
<td>Bolus (one infant) Continuous Formula and/or breast milk</td>
<td>Decreased % gastric residuals before next feeding (p = .008) Decreased vomiting (p = .008) Increased weight gain among vomiting infants</td>
<td></td>
</tr>
<tr>
<td>Vandenplas, Sacre, Loeb (1981)</td>
<td>Open case series</td>
<td>20</td>
<td>29–36 [34]</td>
<td>920–2,440 [1,435]</td>
<td>3–35 [11]</td>
<td>0.1 mg/kg eight x day</td>
<td>5–3 (duration decrease) Slow continuous over 15–30 minutes</td>
<td>Standard or premature formula</td>
<td>Decreased gastric residuals Decreased vomiting Increased feeding volume Decrease in all GER* parameters measured (pH monitoring, number and length of reflux episodes)</td>
<td></td>
</tr>
</tbody>
</table>

*GER = gastroesophageal reflux
sphincter tone. The improved intestinal motility leads to rapid small and large bowel transit times. Both of these mechanisms may be beneficial in infants with bowel dysmotility problems, but they may also have adverse effects by causing diarrhea.

Cisapride is well absorbed orally and becomes highly protein bound. The drug undergoes first-pass metabolism in the liver and gut wall, where it is metabolized by the cytochrome P450 system and excreted in both urine and feces. The specific gastrointestinal action of the drug and the absence of central nervous system side effects make it more acceptable than metoclopramide for use in premature infants.

CISAPRIDE AND FEEDING INTOLERANCE: CLINICAL TRIALS

The role of cisapride in improving gastric motility is well supported. There is, however, a paucity of literature regarding its use in the neonatal population, particularly with respect to its efficacy in reducing feeding intolerance in this group of patients. An extensive literature search identified only three studies concerning the use of cisapride in premature infants experiencing feeding intolerance (Table 1).

Given the limited number of studies identified, none were excluded from the review. The methodologic criterion for the critical assessment of a therapeutic intervention is random assignment of patients to treatments. All studies lacked scientific rigor because subjects were not randomly allocated to treated and control groups. Random allocation eliminates biases that may lead to false results, therefore increasing the likelihood that the results are true—in other words, increasing validity.

The experimental design of the trials could at best be classified as reports or case series with a very limited sample size. The absence of randomization and blinding of the investigators and potential control subjects in these studies allows for a series of potential biases that could have resulted in erroneous conclusions. The trials were, however, reviewed to gain a better understanding of the current state of knowledge regarding the use of cisapride in premature infants experiencing feeding intolerance. Table 2 summarizes these three clinical trials.

In these studies, infants were enrolled when they were not tolerating feeds either because of increased gastric residuals and/or vomiting. All infants had abdominal x-ray studies to rule out organic causes of feeding intolerance (such as necrotizing enterocolitis). The gestational age of infants included in the studies ranged from 26 to 38 weeks. All studies had small sample sizes (14–20). Infants were observed for 24 hours to obtain baseline data, and then cisapride treatment was initiated. There was no blinding in any of the studies. Infants were then observed for an additional 48 to 120 hours.

Feeding protocols were inconsistent and varied from study to study. In one study, infants were on continuous nasogastric feeds. In another study, infants were on slow continuous feeds over 15–30 minutes. In the third study, one infant was on bolus feeds, and the other infants were on continuous feeds. These feeding protocols differ from current practice and are usually reserved for infants who cannot tolerate bolus feeds. Protocol variability also does not permit data comparison of studied patients.

Cisapride administration (dose and duration) also varied across studies. Melis and Janssen used 0.15 mg/kg cisapride, four times a day. Vandenplas, Sacre, and Loeb administered 0.1 mg/kg of cisapride eight times a day. In one study, the duration of administration was decreased from five days to three days because "feeding tolerance seemed good." In another study, an extended duration of administration was used, with the mean duration being 38 days.

Similar outcome measures were reported by all studies and included the following: (1) decreased gastric residuals, (2) decreased incidence of vomiting, (3) increased feeding volume, (4) a decrease in all reflux parameters measured (such as pH monitoring and number of reflux episodes), and (5) increased weight gain, particularly in a group of infants who were vomiting.

One physician from a university hospital in Belgium noticed an increase in cholestasis in his patients treated with cisapride. This prompted Janssens Pharmaceutica, which manufactures cisapride, to issue a warning in 1987 regarding the possibility of cholestasis occurring in premature babies less than 34 weeks gestational age. This warning remains in effect, but the report of cholestasis in premature infants treated with cisapride was not confirmed.

A group of investigators assessed the action and side effects of cisapride on all premature babies treated with cisapride in their unit over a
period of one year. Cholestasis was observed in 4 of 20 premature babies (average gestational age 27 weeks) treated with cisapride. The cause of cholestasis, however, could not be attributed definitively to cisapride because there was a simultaneous outbreak of Candida sepsis, which could have contributed to the incidence of cholestasis.  

Furthermore, in three of the four infants, feeds were initiated very late, and cholestasis was already evident before cisapride was administered. In one of the four infants, cholestasis subsided while he remained on cisapride. Cisapride was discontinued in the other two babies, and cholestasis reversed. In all three infants, liver function tests were normal before discharge. The fourth baby died from Candida sepsis and bronchopulmonary dysplasia. Two of the four infants had transient hypothyroidism. The authors concluded that their findings did not support the claim that cisapride induces cholestasis in premature infants.  

A clinician currently trying to decide whether treatment with cisapride does more harm than good in premature infants is unable to depend on the literature available to review because of the lack of conclusive evidence from proper scientific methodologic trials.

UNANSWERED QUESTIONS

What is the optimal dosage of cisapride and length of treatment for the feeding intolerant premature infant? Answers are not available in the literature and need to be defined by future research. Based on anecdotal evidence, some centers use a cisapride dose of 0.2 mg/kg, three or four times a day, which is the average dose cited in the literature. Cisapride therapy is usually continued until the infant reaches 40 weeks postconceptional age.

Very few adverse effects of cisapride are documented in the recent research literature. The adverse reactions that are described are minor. Reported side effects include transient diarrhea, abdominal cramping, and eructation. At one time, it was thought that cisapride might be associated with an increased incidence of cholestasis, but follow-up studies did not substantiate this assertion (as previously discussed).

RECOMMENDATIONS

The role of the neonatal nurse is crucial in assessing the relevant clinical outcomes of cisapride therapy. However, the current state of research limits interpretation regarding the efficacy of cisapride in reducing the rate of feeding intolerance in premature infants. Randomized double blind controlled clinical trials that compare treatment (cisapride) and control (placebo) groups are necessary to determine accurately the effect of cisapride on reducing the incidence of feeding intolerance in premature infants. In the meantime, neonatal nurses need to monitor with great vigilance those premature infants who are prescribed cisapride by observing the following measures:

- Monitor and document changes in stool pattern (diarrhea). If stools are watery and frequent, these changes need to be reported to the neonatal clinician.
- Observe for changes in temperament, such as irritability, which may be related to abdominal cramping, after the initiation of cisapride. Changes in behavior should be documented and reported. In the two previous instances, the dose of cisapride may need to be reduced or the drug discontinued.
- As the infant gains weight, ensure that the dose of cisapride is adjusted to keep up with the baby’s weight gain. If an infant who is on cisapride and tolerating feeds becomes intolerant of feeds, the nurse should check the dosing regimen to confirm that the infant is receiving the appropriate dose per kilogram of body weight.
- Closely monitor the infant for clinical signs of jaundice (such as lethargy and poor feeding), and, once again, document and report these signs to the neonatal clinician.

REFERENCES


**About the Authors**

Sinhae Premji is a clinical nurse specialist/neonatal practitioner at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario, Canada. In addition to her clinical responsibilities, she is a clinical lecturer in the School of Nursing at McMaster University, Hamilton, and an instructor for the perinatal program at Mohawk College, Hamilton, Ontario. She received her BScN from McMaster University, her MSc from University of Toronto, and is currently working on her doctorate in clinical health sciences (nursing) at McMaster University.

Jennifer Wilson is a clinical nurse specialist/neonatal practitioner at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario. She received her BScN and MHSc from McMaster University in Hamilton, Ontario. She is also a clinical lecturer in the School of Nursing at McMaster University and an instructor for the perinatal program at Mohawk College, Hamilton, Ontario.

Reta Pass is the director of nurseries at St. Joseph’s Hospital, Hamilton, Ontario, professor of pediatrics (neonatal division) at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario, and a course instructor in the expanded role nursing program at the master’s level of neonatology. He received his fellowship from the Royal College of Physicians, Canada, and is also a fellow of the Royal College of Physicians, Dublin, Ireland.

Shari Gray is the neonatal clinical pharmacist at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario. She received her BScPharm from the University of Toronto. She teaches neonatal pharmacology to residents, pharmacists, and nurse practitioner students.

For more information, please contact:

Shahirose S. Premji, MSc(N)
Clinical Nurse Specialist-Neonatal Practitioner
Neonatal Unit 4G MUMC
Children’s Hospital
Hamilton Health Sciences Corporation
1200 Main Street West
Hamilton, Ontario L8N 3Z5
(905) 521-5025
FAX (905) 521-5007
E-mail: Premji@hsc.on.ca
Appendix B-4

January 18, 2000

Judyann Silbo
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Shabirose S. Premji, Ph.D.(c)
Clinical Nurse Specialist/Neonatal Practitioner
Hamilton Health Sciences Corporation
Children’s Hospital Neonatal Unit - MUMC 4G
1200 Main St. West
Hamilton, Ontario
L8N 3Z5
Phone: (905) 521-5025
Fax: (905) 521-5007
E-mail: premj@hhsc.ca
Cisapride: The Problem of the Heart

Shahirose S. Premji, RN, MSc(N)
Bosco Paes, MD, FRCPI, FRCPC

Cisapride has been used in the neonatal population as a first-line gastrointestinal prokinetic agent for managing feeding intolerance secondary to decreased gastrointestinal motility. It is manufactured in Canada under the trade name Prepsulid by Janssen-Ortho Inc. and in the U.S. as Propulsid by Janssen Pharmaceutica. Feeding intolerance presents as abdominal distention, vomiting, and feeding residuals. It reflects a delay in the maturation of the neonate’s motor activity in the gut. Although feeding intolerance is time limited, it can take up to four weeks to resolve. Cisapride is thought to be efficacious in the management of infants with feeding intolerance. This is because it enhances gastric motility, facilitating earlier establishment of full oral feedings and possible discharge from the hospital. The cost savings to both the parents and the health care system may be substantial, given the improved survival rates for neonates with a birth weight of 500 to 700 gm, and the previously reported 67 percent incidence of feeding intolerance in this cohort of infants. This may in fact be an underestimate of the problem.

In the premature infant population, cases of prolonged QT interval secondary to cisapride have been reported. Proarrhythmic effects of cisapride have been documented in patients who receive cisapride alone or with concomitant use of drugs such as antibiotics (e.g., erythromycin). These proarrhythmic effects, however, may go unnoticed because sign or symptoms may be absent.

Abstract

Cisapride has been used in the neonatal population as a first-line gastrointestinal prokinetic agent for managing feeding intolerance secondary to decreased gastrointestinal motility. Cisapride acts specifically at many levels of the gastrointestinal tract and has no central nervous system side effects. Recently, prolonged QT interval has been reported secondary to high-dose cisapride, and concerns regarding its use in premature infants have been raised. In response, Janssen-Ortho Inc. and Janssen Pharmaceutica, the manufacturers of cisapride in Canada and the U.S., have released safety information prohibiting the use of cisapride in premature infants. In light of the present evidence, it is imperative that NICUs that continue to prescribe cisapride for the management of feeding intolerance exercise vigilance in cardiac monitoring and recognize the importance of drug interactions that lead to elevated cisapride levels.

Product Safety Information

In Canada, Janssen-Ortho Inc. circulated important safety information, in a letter dated July 22, 1997, to all health care professionals regarding the use of cisapride in premature infant. The letter stated: "PREPULSID is contraindicated in premature born infants (born at gestation age of less than 36 weeks), from 0 through three months after the delivery date." Additional revisions to the prescribing information, which does not include a comprehensive list of drugs, are as follows:

The concomitant oral or parenteral use of the following potent cytochrome P450 3A4 inhibiting drugs...
may lead to elevated PREPULSID (cisapride monohydrate) blood levels and is contraindicated.

**Antifungals:** Oral or I.V. fluconazole, itraconazole, ketoconazole

**Antibiotics:** Oral or I.V. erythromycin, clarithromycin

**Protease inhibitors:** Ritonavir, indinavir (in vitro studies suggest that aminonavir is only a weak inhibitor)

Potential benefits should be weighed against risks prior to the administration of PREPULSID (cisapride monohydrate) to patients who have, or may develop prolongation of cardiac conduction intervals, particularly QTc. In addition, patients with or suspected of having the above risk factors should be evaluated prior to the administration of cisapride. An ECG should be considered as part of this evaluation to exclude a prolonged QT interval.18

As a result, several NICUs have stopped prescribing cisapride for the management of feeding intolerance in premature infants. In special circumstances, parental consent has been obtained, and a baseline electrocardiogram (ECG) has been performed prior to initiation of cisapride therapy. In the U.S., a similar warning about safety issues with cisapride was circulated on June 26, 1998, by Janssen Pharmaceutica and the U.S. Food and Drug Administration.15

**CISAPRIDE**

**Mechanism of Action**

Cisapride, a highly protein-bound drug, is well absorbed orally and undergoes first-pass metabolism in the liver and gut wall. There it is metabolized by the cytochrome P450 system and is excreted in both urine and feces.8,19 Cisapride acts at many levels of the gastrointestinal tract. First, it increases esophageal peristaltic activity and enhances esophageal sphincter tone, thereby decreasing gastric reflux into the esophagus. Second, it accelerates gastric emptying by improving gastric and duodenal contractions. Finally, it stimulates gastric motility in a way that mimics the natural progression of maturation of the migrating motor complex. More specifically, cisapride acts at the myenteric plexus of the intestine, causing physiologic release of acetylcholine. Rapid large- and small-bowel transit times result from the improved intestinal motility.19,20

**Dose and Route**

Unlike data for the adult population,8,19 age-appropriate pharmacokinetic data for cisapride use in the neonatal population are not well defined. The efficacy and safety of cisapride, however, have been demonstrated in pilot studies on a total of 54 premature neonates.5-7 These findings should be used to stimulate larger, well-designed, experimental trials.12 Optimal dosage of cisapride and length of treatment for the feeding-intolerant premature infant are also not known and need to be defined in future research.

Our center, which is a 34-bed NICU in a university-affiliated teaching hospital, commonly used a cisapride dose of 0.2 mg/kg/dose given orally, three or four times a day, for infants <1,500 gm. This is the average daily dose (0.8 mg/kg/day) based on the current literature. Cisapride therapy was usually continued for four weeks or until the infant reached 40 weeks postconceptional age. In accordance with Janssen-Ortho Inc. safety recommendations, the use of cisapride early in the postnatal course has been discontinued in this population of infants since September 10, 1997.17 Once these infants reach three months corrected age, however, the same dose and frequency of cisapride become applicable for the management of feeding intolerance. Intravenous cisapride is available for adult use, but it is not currently administered to neonates.

**Adverse Effects**

Cisapride is the preferred prokinetic agent in the neonatal population because of its specific gastrointestinal action and because it has no central nervous system side effects. In July of 1997, Janssen-Ortho, manufacturer of the drug, issued a warning in Canada against use in newborns <36 weeks gestational age and <3 months postnatal age. “The warning noted that variable pharmacokinetics could potentially lead to cardiac toxicity.”15 In December of 1997, members of national organizations such as the American Academy of Pediatrics Committee on Drugs, the Committee on the Fetus and Newborn, and the Section on Perinatal Pediatrics were asked to provide information about the toxicity of this drug. They were unaware of severe and frequent cisapride toxicity in premature infants, so a retrospective study was undertaken. It concluded that the frequency of severe side effects is <1 in 11,000 patients, but that the retrospective data may cause this figure to be lower than the actual incidence. They recommended further randomized, controlled studies “to evaluate the cardiac response of newborn infants to cisapride.”15 Use of cisapride remains more acceptable than use of other prokinetic agents, such as metoclopramide.19

In the general population, the incidence of adverse reactions with cisapride use is low, and its side effects are minor. Adverse reactions include transient diarrhea, abdominal cramping, and borborygmi.21 The recent retrospective survey of neonatology training program directors in the U.S. (n = 105) revealed that, of 58,000 premature infants <36 weeks gestation admitted to 46 NICUs (response rate 44 percent), 19 percent were treated with cisapride. Among the 11,149 infants treated, 3 who were treated for gastrointestinal reflux had nonfatal arrhythmias. Two of these infants had bradycardic arrhythmias requiring resuscitation, and the third had a similar transient episode. The former 2 infants had received a tenfold dose of cisapride—that is, 2
mg/kg instead of 0.2 mg/kg. The third infant had received erythromycin in addition to cisapride. The authors concluded that their “survey did not confirm an increased frequency of serious arrhythmias in premature newborns compared with adults” (p. 471). Data regarding the safety of cisapride in the neonatal population are confined to the monitoring of cholestasis, and research has failed to substantiate the assertion that cisapride might be associated with an increased incidence of this condition. Despite limitations of the research with regard to the efficacy and safety of cisapride, the drug continues to be used worldwide in NICUs.

IMPLICATIONS OF PROLONGED QT INTERVAL

An arrhythmia is an irregularity of cardiac rate and rhythm. A prolonged QT interval is indicative of slow ventricular repolarization. It can lead to ventricular arrhythmias, such as torsade de pointes. Tachycardia is a morphologic characteristic of torsade de pointes. It can cause sudden death.

There are two categories of prolonged QT interval: idiopathic and acquired. Idiopathic prolonged QT interval, the more prevalent category, represents a congenital disorder; it can occur sporadically or may be familial. The heart is structurally normal; however, affected individuals develop life-threatening ventricular tachyarrhythmias, including torsade de pointes, with great variability among individuals. Mortality varies among families. After the initial syncope, overall mortality among untreated symptomatic patients is 20 percent in the first year and 50 percent within ten years.

Acquired prolonged QT interval results from electrolyte disturbances (hypocalcemia, hypokalemia), hypothermia, central nervous system injury, malnutrition, or medications—e.g., macrolide antibiotics such as erythromycin. Cisapride-induced prolonged QT interval has been reported, and according to Levin and colleagues, “the manufacturer estimates the rate of serious ventricular arrhythmias is one per 120,000 patients (information obtained from the spontaneous reporting system in the United States)” (p. 280). The retrospective survey of neonatology training program directors in the U.S. estimated the rate of serious adverse events in premature infants to be less than 1 per 11,000 patients. However, this estimate may not accurately represent the true incidence of adverse effects because of the poor response rate of the survey (44 percent) and recall bias associated with a retrospective study design. The rate of serious adverse events in premature infants may actually be higher. According to Ward and colleagues, “this frequency of adverse events would not appear to justify a warning against cisapride treatment of premature newborns and young infants at this time” (p. 472).

The potential cardiac effect of cisapride is to increase the heart rate. At present, the proarrhythmic effect of cisapride—that is, the mechanism by which it affects ventricular repolarization—is unclear.

REVIEW OF LITERATURE CONCERNING PROARRHYTHMIC EFFECTS OF CISAPRIDE

In the literature, cases of prolonged QT interval secondary to cisapride have been reported in the premature infant population. The dose of cisapride was higher—1 to 1.6 mg/kg/day—in these case reports than that used in our NICU, which was 0.8 mg/kg/day. The prolonged QT interval reversed to normal when treatment was discontinued or when the dosage was reduced to 0.8 mg/kg/day. Transient bradycardic arrhythmia has been reported in one patient with concomitant use of erythromycin and cisapride. Cisapride may cause prolongation of ventricular repolarization in children in the absence of signs or symptoms. Hence, the case reports in the literature may not be isolated events, and the potential silent nature of this side effect should be taken seriously.

Accidental overdose has also been reported in the literature, the dosing error being tenfold. Hanson and colleagues report a case in which a six-week-old female infant was given 2 mg/kg instead of 0.2 mg/kg, four times per day, for 48 hours. Although the infant remained entirely well, the clinical exam revealed a soft systolic ejection systolic murmur over the pulmonary area and a heart rate of 140 beats per minute (bpm). ECG findings included sinus rhythm, right-axis deviation, a partial right bundle branch block pattern, a corrected QT interval of 497 milliseconds (msec) with T wave flattening, and prominent U waves. Mild pulmonary stenosis was revealed on the echocardiogram. The cisapride therapy was discontinued. Within 21 hours, the QT interval was shortened to 436 msec, and the heart rate decreased to 117 bpm.

Enriquez and colleagues conducted a randomized, double-blind, placebo-controlled study using low-dose cisapride (0.8 mg/kg/day) on 34 infants of ≤32 weeks gestation. All subjects had ECG recordings at the beginning and at the completion of the study. No rhythm disturbances were noted in the infants in the cisapride group; that is, the mean QT intervals were within normal range for age at the two time periods. Because frequent ECG recordings were not performed, transient changes in QT interval may have been missed. The uncertainty regarding the binding of ECG interpretations further precludes us from generalizing from this study data regarding the occurrence of prolonged QT interval with cisapride use. The study is also limited by its small sample size, which was based on the outcome measure of time to reach full feedings rather than on the incidence of cisapride-induced QT prolongation, which according to Griffin is very low in the pediatric population.

NURSING IMPLICATIONS

As we accumulate a knowledge base, with ongoing publi-
tations of anecdotal cases of prolonged QT interval associated with cisapride therapy, continuous monitoring of QT intervals before, during, and after therapy may be warranted in the future. At present, however, it is important that great caution be exercised in the use of cisapride. For neonates in particular, the dosage of cisapride should not be greater than 0.8 mg/kg/day. Frequent ECG recordings are recommended; a baseline recording should be obtained before therapy is initiated.

The potential for life-threatening toxic effects is exemplified by the case of accidental overdose previously described. This raises questions concerning the safety of using cisapride in the pediatric population. Drugs that inhibit the action of the cytochrome P450 system (such as fluconazole and erythromycin) may elevate serum levels of cisapride, increasing the risk of cardotoxic effects. It is imperative that the risks and benefits of using these drugs concomitantly with cisapride in the treatment of infants be reappraised. Where possible, the use of such drugs should be discontinued to avoid elevated levels of cisapride. Where there is concomitant use of drugs that may influence the metabolism of cisapride, the importance of screening for ECG abnormalities becomes crucial. Because 50 percent of children often go home on cisapride, it is essential to educate parents on potential side effects and drug interactions.

From the clinical perspective, one is left to explore alternative strategies for the management of feeding intolerance in the preterm infant. These may include giving smaller, more frequent, bolus feedings; giving continuous nasogastric tube feedings; and placing the infant in the upright position during feeding. The use of other, safer, prokinetic agents, such as low-dose erythromycin, should be further explored. Regular-dose erythromycin can have adverse effects, including diarrhea, vomiting, and arrhythmias. But these may not pertain to the dose recommended for the management of feeding intolerance. Neither is it known how the widespread use of low-dose erythromycin may alter an infant’s established normal bacterial flora and result in pathogens resistant to antibiotics, or how this widespread use may affect the incidence and type of nosocomial infections in the NICU setting. Low-dose erythromycin appears promising in case reports. However, definitive answers to these questions must await the results of large, randomized, controlled trials.

REFERENCES

About the Authors

Shahirooe Premji is a clinical nurse specialist/neonatal practitioner at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario, Canada. In addition to her clinical responsibilities, she is an assistant clinical professor in the School of Nursing at McMaster University, Hamilton. She received her BScN from McMaster University, her MS from the University of Toronto, and is currently working on her doctorate in clinical health sciences (nursing) at McMaster University.

Bonnie Fass is the director of nurseries at St. Joseph’s Hospital, Hamilton, Ontario; professor of pediatrics (neonatal division) at Hamilton Health Sciences Corporation, McMaster Site, Hamilton, Ontario; and a course instructor in the expanded role nursing program at the master’s level of neonatology. He received his fellowship from the Royal College of Physicians, Canada, and is also a fellow of the Royal College of Physicians, Dublin, Ireland.

The authors would like to dedicate this article to the late Shrinibai Abdulrasul Kassam Khimji. May her soul rest in eternal peace.

For further information, please contact:
Shahirooe S. Premji, RN, MSc(N)
Clinical Nurse Specialist/Neonatal Practitioner
HHSC, Children’s Hospital Neonatal Unit—4G MUMC
1200 Main Street West
Hamilton, Ontario
Canada L8N 2Z5
(905) 521-5025 FAX (905) 521-5007
E-mail: Premji@exchangelm.cmhh.on.ca

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Appendix C

Modified Bell Staging Criteria For Necrotizing Enterocolitis
Modified Bell Staging Criteria for Necrotizing Enterocolitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>Systematic Signs</th>
<th>Intestinal Signs</th>
<th>Radiologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Suspected NEC</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Increased pregavage residuals, mild abdominal distention, emesis, guaiac-positive stool</td>
<td>Normals or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>IB</td>
<td>Suspected NEC</td>
<td>Same as above</td>
<td>Bright red blood from rectum</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>Proven NEC - mildly ill</td>
<td>Same as above</td>
<td>Same as above, plus absent bowel sounds, with or without abdominal tenderness</td>
<td>Intestinal dilation, ileus, pneumatosis intestinals</td>
</tr>
<tr>
<td>IIB</td>
<td>Proven NEC - moderately ill</td>
<td>Same as above, plus mild metabolic acidosis and mild thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite abdominal tenderness, with or without abdominal cellulitis or right lower quadrant mass</td>
<td>Same as IIA, plus portal vein gas, with or without ascites</td>
</tr>
<tr>
<td>IIIA</td>
<td>Advanced NEC - severely ill, bowel intact</td>
<td>Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia</td>
<td>Same as above, plus signs of generalized peritonitis, marked tenderness, and distention of abdomen</td>
<td>Same as IIB, plus definite ascites</td>
</tr>
<tr>
<td>IIIB</td>
<td>Advanced NEC - severely ill, bowel perforated</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as IIB, plus pneumoperitoneum</td>
</tr>
</tbody>
</table>


Abbreviation: necrotizing enterocolitis (NEC)
Appendix D

Classification of Intrauterine Growth Restriction
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<th>Gestational Age (weeks)</th>
<th>10th Percentile (grams)</th>
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</tr>
<tr>
<td>25</td>
<td>&lt; 563</td>
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Appendix E

Record Form For Data Collection Related to Maternal History, Mode of Delivery, and Infant Characteristics
INFANT DATA SHEET

Case # ____________________
ID Number ____________________
Birth Date Day ____ Month ____ Year ____
Admission Date Day ____ Month ____ Year ____
Gestational Age _______ completed weeks
Birth Weight _______ grams
Gender _______ Female _______ Male
Birth Number _______ Singleton _______ Twin _______ Triplet _______ Quadruplet
Transferred From Another Hospital After Birth _______ Yes _______ No
C-Section _______ Yes _______ No
Vaginal Delivery _______ Yes _______ No
Rupture of Membranes for Greater Than 24 hours _______ Yes _______ No
Abruptio or Previa _______ Yes _______ No
Eclampsia, Preeclampsia _______ Yes _______ No
Celestone _______ Yes _______ No Multiple Course _______ Yes _______ No
Apgar Score at One Minute _______ Apgar Score at Ten Minutes _______
Apgar Score at Five Minutes _______
Diagnosis

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
Age When Feeds Commenced _______ days
TIPP Study _______ Yes _______ No
PDA _______ Yes _______ No
Indomethacin  _____ Yes   _____ No
Intraventricular Hemorrhage  _____ Yes   _____ No
Low Blood Pressure (Tx Normal Saline/Dopamine)  _____ Yes   _____ No
Oxygen Requirement  _____ days
Ventilation Requirement  _____ days
Nasal Prong CPAP  _____ days
Umbilical Arterial Catheter  _____ days
Umbilical Venous Catheter  _____ days
Appendix F

Record Form For Data Collection of Variables Related to Feeding
Appendix G

Ethical Approval
June 17, 1998

PROJECT NUMBER: 98-164

PROJECT TITLE: "Feeding practice guidelines for premature infants less than 1500 grams: efficacy and safety"

PRINCIPAL INVESTIGATOR: Shahirose Premji

This study was considered at the June 16, 1998 meeting of the Research Ethics Board; the submission was found to be acceptable on both ethical and scientific grounds.

PLEASE QUOTE THE ABOVE-REFERENCED PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE.

Yours sincerely,

[Signature]

For: David L. Streiner, Ph.D.
Chair, Research Ethics Board

/sk