UK AND NORTH AMERICAN NEONATAL FEEDING SURVEY

A survey of practice in the feeding of preterm and very low birth weight infants with particular reference to necrotising enterocolitis

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ABSTRACT

The safe and timely introduction of milk feeding is a fundamental part of neonatal care for preterm and low birth weight infants. Yet enteral feeding in such infants presents significant challenges for the neonatologist. Data from randomised controlled trials are sparse and there is limited evidence to guide clinical practice. Opinion about optimum feeding regimens varies considerably and this variation in opinion is likely to be reflected in similar variation in clinical practice. Different approaches to feeding appear to carry different risks and benefits and serious adverse clinical outcomes may accompany extremes of practice in this area.

Much of the uncertainty around practice in enteral feeding has been engendered by inconsistent results from research studies. Most studies have centred upon necrotising enterocolitis (NEC), a serious and devastating bowel disease that primarily affects preterm infants. Mortality from NEC is high. The aetiology of the condition remains elusive and is likely to be multifactorial, but early and rapid enteral feeding has been implicated. In contrast, delayed feeding necessitating prolonged use of central venous catheters and parenteral nutrition may increase susceptibility of preterm infants to severe systemic infection. The potential role of enteral feeding in the development of NEC is of great interest because unlike many other factors, it is amenable to change. However, only through well-designed trials of different practice will optimum strategies for feeding in high-risk infants begin to emerge. The design of acceptable and feasible clinical trials that fall within the known margins of safety is challenging. As studies of neonatal feeding practice would probably need to take place on an international basis to provide sufficient numbers of outcomes, disparities in practice between different countries may serve only to increase this challenge. An understanding of the variation in practice, the factors influencing this variation and the effects on feed-related outcomes is necessary to inform further research.

There have been few recent detailed reports relating to opinions about feeding of preterm infants. No previous study has explored the relationship between available research evidence, clinician opinion and clinical practice. The subject of this thesis is a two-part observational study, conducted in the United Kingdom (UK) and Canada. A questionnaire survey sent to neonatal clinicians sought to investigate current opinion and reported practice with respect to enteral feeding of infants born at less than 30 weeks of gestation and/or

1501g birth weight in the UK and Canada. This survey was complemented by a detailed retrospective review of the medical and nursing records of infants admitted to fifteen UK and three Canadian neonatal units. Opinions of neonatal clinicians were described and factors influencing feed-related decisions were explored. Analysis of infant feeding data allowed comparison and contrasting of different practices and exploration of short-term neonatal outcomes that may be related to or influenced by variation in practice.

Questionnaire responses of 302 clinicians and feeding data from 670 infants were analysed. The results of the study confirmed wide variation both in opinion and in clinical practice across almost all aspects of enteral feeding. This was evident between and within neonatal units and between the two countries. Reported availability and clinicians' awareness of written guidelines to assist in decision-making were also extremely variable. The study demonstrated that a large number of factors appear to influence feeding practice, but that these, too, differ between countries. The most consistent influence affecting the advancement of enteral feeds was the presence of signs consistent with actual or suspected intra-abdominal pathology such as NEC. Occurrence of proven NEC and associated mortality were within previously reported ranges.

The effects of variation on necrotising enterocolitis and other important clinical outcomes are not known. Important gaps in knowledge remain with respect to the rate of feed advancement and the relationship between therapeutic interventions and NEC. Further research is required and should be directed towards defining optimum feeding strategies that maximise benefits in terms of growth and neurodevelopment, whilst minimising morbidity and mortality associated with NEC and infection.

Declaration

I declare that I have composed this thesis and the results presented are a product of my own work.

Signed .

Elaine M Boyle

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PART I

INTRODUCTION AND BACKGROUND

CHAPTER 1

INTRODUCTION

Enteral feeding of preterm and very low birth weight infants presents significant challenges for neonatologists. Current opinion about optimum feeding regimens varies considerably. Sources of variation are many: timing of introduction of milk feeds, type of milk used, rate of progression to full milk feeds, frequency of feeds; feeding by bolus or continuous methods, the use of minimal enteral feeding regimens and management of feed intolerance. It is therefore highly likely that this variation in opinion is reflected in equally wide variation in clinical practice, both between and within neonatal units (NNUs) worldwide.

In clinical decision-making about preterm infant feeding, there are many factors to consider. Different approaches to feeding appear to carry different risks and benefits and careful evaluation of these is required. Serious but conflicting clinical risks may accompany extremes of practice in this area.

Much of the uncertainty around optimal methods of feeding has been engendered by inconsistent results from research studies. Most studies to date have centred upon necrotising enterocolitis (NEC), a serious and life-threatening bowel disease that primarily affects preterm infants. The potential influence of the timing of introduction and advancement of enteral feeds in the development of this disease is a major concern for clinicians in neonatology. However, recruitment of infants is often a challenge for interventional research studies in neonatal medicine, due to the difficulties of approaching parents for consent at a very stressful time and the relatively small numbers of preterm infants. Although there is now a substantial amount of published work on the subject of enteral feeding, much of this was carried out a considerable number of years ago. This, together with small numbers of subjects, makes results difficult to interpret. In addition, many of the interventional and epidemiological studies have been carried out in North America, where data from larger numbers of infants are available than in the United Kingdom (UK). Many British clinicians have regarded these studies as having little relevance for them since some study interventions have borne little resemblance to current UK trends in practice.

A pilot survey of feeding practice conducted in Scottish NNUs was the subject of Dr Elaine Boyle's dissertation for a MSc in Epidemiology[1 2] and confirmed wide inter-unit variation in

both opinion and practice of clinicians in the feeding of infants born between 23 and 32 weeks of gestation. It was not large or detailed enough to explore the relationships between feeding practices and important outcomes such as the incidence of NEC and the occurrence of catheter related sepsis.

Optimum strategies for feeding in high-risk infants can only be identified from the results of well-designed trials of different practice. However, given the current disparities in practice, it is challenging to design trial protocols that will be acceptable to large numbers of clinicians and feasible to carry out, that fall within the known margins of safety and that examine the most appropriate major outcomes. Large international multicentre trials usually yield more reliable and generalisable results than small, single-centre studies. However, as studies of neonatal feeding practice would probably need to take place on an international basis to provide sufficient numbers of outcomes the variation in clinical practice in different countries of the world will make the study design and feasibility even more challenging.

This observational study, carried out in NNUs in the UK and Canada, aimed to examine the evidence base for early enteral feeding of preterm and low birth weight infants. In the light of this published literature, it aimed to describe opinions of neonatologists with regard to enteral feeding, document the approaches used, identify any extremes of practice and consider how short-term nutritional outcomes and the occurrence of NEC relate to this practice.

1.1 Hypothesis

It was anticipated that this survey would demonstrate very limited availability of written feeding guidelines and wide variation in many aspects of feeding practice in neonatal units in the UK. A further specific hypothesis was that enteral feeds would be introduced later and advanced more slowly in Canadian neonatal units than UK units.

CHAPTER 2

AIMS AND OBJECTIVES OF THE RESEARCH

2.1 General Aims

To describe the variation in opinion and clinical practice in UK and Canadian NNUs with respect to the enteral feeding of preterm and very low birth weight infants and to assess the relationship between feeding interventions and important short-term outcomes, with particular reference to NEC, in order to inform subsequent trials.

2.2 Specific Objectives

1. To determine factors that influence UK and Canadian clinicians' decision-making with respect to the initiation, progression and discontinuation of enteral feeds in infants who are born at less than 30 weeks of gestational age or with a birth weight of less than 1501grams.

2. To describe clinical practice in UK and Canadian NNUs with respect to enteral feeding in infants who are born at less than 30 weeks of gestational age or with a birth weight of less than 1501grams.

3. To explore the relationships between different approaches to enteral feeding, short-term nutritional outcomes and NEC in infants who are born at less than 30 weeks of gestational age or with a birth weight of less than 1501grams.

4. To identify areas of practice worthy of further investigation.

CHAPTER 3

BACKGROUND AND REVIEW OF THE LITERATURE

The aim of this literature review is to summarise the available background knowledge related to enteral feeding of preterm infants and the benefits and risks, associated with feeding practice in the clinical setting. In view of the large number of themes of interest and relevance to this area of clinical practice, a comprehensive systematic review of the literature in each of these domains is beyond the scope of this thesis. The following review is therefore a careful review of the published literature describing research into feeding practice in preterm neonates and its associated complications, primarily NEC. Literature searches for all sections were carried out using Medline for the years 1966 to the present date via Pub-Med. Search terms used were "infant, premature", "infant, newborn" "infant feeding", "enteral nutrition", "breastfeeding", "human milk", "breast milk", "human milk fortifier" "enterocolitis, necrotizing", "gastro-oesophageal reflux", "feed advancement", "feed interval", "preterm formula", "feed intolerance", "patent ductus arteriosus", "blood transfusion" and "indomethacin". Searches were limited to "human" and to the age range "newborn; birth to one month" and to literature published in the English language. Titles of all references retrieved were reviewed and the relevant papers examined. Additional references were identified from reference lists of these papers.

3.1 Pathophysiology of NEC

Despite extensive basic science and clinical research over many years, the pathogenesis of NEC remains poorly understood. The disease is predominantly one of newborn infants and produces severe necrosis of the intestine. NEC has not been described in stillborn infants[3] and therefore it is presumed that at least some factors leading to development of the disease are acquired after birth. The newborn gut, and in particular the preterm gut, appears to be susceptible to a number of important pathogenic mechanisms that have been proposed as important factors involved in the development of the pathological features of NEC. However, the complex events predisposing infants to NEC are thought to be multifactorial and have not yet been clearly defined.

3.1.1 Role of hypoxia-ischaemia

Ischaemia of the gut has long been implicated in the development of NEC. Histopathology of resected portions of gut from infants with the disease demonstrates coagulative necrosis, a feature of ischaemic damage. Early epidemiological studies of NEC noted a higher incidence of the disease in mature infants suffering a significant perinatal asphyxial insult[4-6]. These findings led to the hypothesis that asphyxia in such neonates produces the "diving reflex", which describes redistribution of blood flow to the brain and heart, leaving the intestine and other organs relatively hypoxic. This was thought plausible, in that the most common site for NEC in the bowel is the ileocolic region, which is situated at a distance from the superior mesenteric artery, from which it receives its blood supply via smaller branches. NEC in term infants tends to develop early in life, supporting the hypothesis that hypoxia-ischaemia may play a primary role; however, other clinical studies have failed to show an association between asphyxia and NEC[3 7 8]. Many animal models of NEC have been developed based on this concept of ischaemic aetiology and are currently used despite the conflicting evidence[9]. In preterm infants, the disease develops later, suggesting that there may be a different mechanism for the ischaemic changes seen. Although it is accepted that ischaemia has a role in the pathogenesis of NEC, it is not thought to be the primary factor promoting disease.

3.1.2 The immature intestinal circulation

Regulation of the intestinal circulation depends on the peptide, endothelin-1 (ET-1), which has a vasoconstrictor effect[10], and on nitric oxide (NO), a vasodilator[11]. Intestinal production of NO develops *in utero* in response to nitric oxide synthase, produced by the endothelium; production increases in the postnatal period promoting vasodilatation to cope with the large blood flow demands of the maturing newborn intestine. Thus, any endothelial damage may disrupt this process, leading to reduction in blood flow and tissue oxygenation. Studies have shown that premature neonates with NEC have decreased activity of nitric oxide synthase, supporting the hypothesis that disturbance in this mechanism may, at least in part, be involved in the development of NEC[12].

ET-1 has also been linked to NEC where an ischaemic insult has been followed by reperfusion[13]. In this situation, constriction of the intestinal vessels was observed in the gut of immature, but not older individuals. In a study that used a neonatal rat model, animals

were exposed to artificial milk feeding, hypothermia and hypoxia, factors that have been associated with NEC. This produced a reduction in gut blood flow which was greater in rat pups that developed NEC[14].

3.1.3 Immaturity of intestinal barrier function

One of the most important functions of the intestinal epithelium is to provide a barrier between the gut lumen and the rest of the body. The mature gut uses a number of defence systems, both physical and chemical, to protect it from effects of potentially damaging antigens and colonisation with pathogenic bacteria.

Multiple components contribute to the physical barrier. Tight junctions between intestinal cells help to form a mechanical barrier and production of mucus from goblet cells provides further protection. Effective peristaltic propulsion of gut contents avoids stasis and overgrowth of bacterial pathogens. All these systems are immature, even in term infants and correspondingly more so in the preterm neonate, making them particularly vulnerable to gut pathology. Studies have shown that gut permeability is increased in preterm infants during the first two days of life, which may render the gut susceptible to damage from pathogenic bacteria or other injurious insults, although permeability decreases by six days of life[15]. Increased permeability is more obvious in infants with NEC[16]. Epidermal growth factor (EGF) is also important in the function of the intestinal barrier by enhancing proliferation of intestinal epithelial cells in response to injury. Decreased levels of EGF have been noted in preterm infants with NEC[17].

Antimicrobial peptides, lysozyme and phospholipase A2 are secreted from Paneth cells in the crypts of the intestinal wall. These contribute to the biochemical barrier of the gut by regulating the presence and type of bacteria within the intestine[18]. Antimicrobial peptides have antimicrobial activity against many different organisms, including bacteria, fungi and viruses[19 20]. The role of these chemical defences in protection against NEC has not been fully explored in preterm neonates.

It is likely that disruption of these normal protective mechanisms in the gut may predispose to injury and that immature systems may be at greater risk from such damage, which may lead to invasion of pathogenic bacteria with subsequent harmful inflammatory changes.

3.1.4 Role of infection

An infective aetiology has been suggested for NEC and clinically, severe NEC is often almost indistinguishable from overwhelming sepsis in the preterm neonate. The pathological changes of NEC in the intestine only occur postnatally and it has not been identified in stillborn infants, where the gut is sterile[3]. Although most cases are sporadic, outbreaks and clusters of cases have been reported, in patterns typical of infectious diseases[21-23]. Although many cultures taken from infants with NEC are negative for bacteria, organisms have been isolated in blood and stool cultures, sometimes at times of outbreaks, lending further support to this hypothesis[24 25]. Yet no specific organism has been consistently implicated in the pathogenesis of NEC and the majority of cases do not occur in clusters, making it unlikely that NEC is primarily an infectious disease. However, some viral gastrointestinal illnesses present with clinical signs that are difficult to differentiate from those of NEC suggesting that, although the causes may be different, the final pathway in the pathogenesis may be similar in the two conditions[26 27]. Increased occurrence of gastrointestinal illness during outbreaks of NEC or NEC-like illness have been noted in overcrowded NNUs, which might be more in keeping with a disease of viral aetiology[28].

However, the likelihood that bacteria play an important role in the pathogenesis of NEC is suggested by the finding of intestinal intramural gas, presumably caused by bacterial fermentation, in many infants with the disease. Bacterial colonisation of the intestine in the healthy neonate begins after birth and the gut may become colonised with both beneficial and harmful bacteria. The process occurs in four phases and is influenced by a number of factors including the mode of delivery and postnatal feeding. Infants delivered vaginally tend to establish gut colonisation earlier than those delivered by caesarean section, due to exposure to a range of bacteria within the vagina and on the perineum. In the first phase, the predominant organisms found in the gut are those from the mother, such as streptococci and coliform bacteria[29]. Thereafter, during establishment of milk feeds, anaerobic bacteria more suited to the intestinal environment begin to emerge, including bifidobacteria, which are found in higher numbers in breast fed infants than formula fed infants. Bifidobacteria outnumber enterobacteria by around 7 days of age. As solid feeds are introduced, numbers of Bacteroides increase and other organisms such as clostridia and enterobacteria become more evident. Changes in the gut flora of breast fed infants are more dramatic at the onset of weaning than those in formula fed infants, since large numbers of aerobic bacteria and bacteroides are seen earlier with formula feeding[30]. By one year of age, the gastrointestinal

flora resembles that of adults. In very low birth weight infants, the pattern of gut colonisation is somewhat different. Enterobacteria and streptococci continue to be the dominant organisms for a longer time, with much smaller numbers of bifidobacteria emerging than in term infants[29]. However, a recent study showed higher levels of bifidobacteria and lactobacillus than had been seen previously and the authors speculate that this may have been related to the early use of unpasteurised breast milk[31]. Within the context of abnormal gut colonisation, the predominant organisms also tend to be virulent[32 33]. This phenomenon is probably related to the intensive care environment, where the use of broad spectrum antibiotics is common, nasogastric tubes form part of routine care, drugs affecting gastric acidity are often administered and the introduction of enteral feeds tends to be delayed[34].

Abnormal gut colonisation may therefore play a significant part in the pathogenesis of NEC and this is supported by a number of studies. Hoy *et al* examined 752 stool samples from 90 infants during a period when 7 definite episodes of NEC were identified[35]. All episodes followed the introduction of nasogastric feeding; enterobacteria were isolated from the stools of 4 cases before the onset of disease and 4 species of Clostridia were isolated from one. A later study also noted the presence of Clostridia in 3 neonates who later developed NEC, but no controls, leading them to suggest that early colonisation with this organism may predispose to the disease[36]. Bjorkstrom *et al* found significantly increased cultures of Klebsiella, Pseudomonas and Proteus in NEC cases than in infants without NEC[31].

The mechanism by which abnormal gut colonisation may contribute to the pathogenesis of NEC is not fully understood, but may be is related to the immaturity of the immune response to bacteria.

3.1.5 Immunity and inflammation

Toll-like receptors (TLRs) are transmembrane proteins located on the surface of host defence cells, which recognise pathogen-associated molecules including glycoproteins, lipopolysaccharides and nucleic acids. TLRs are present in intestinal cells and this means that they may be able to detect, within the lumen, components of bacteria such as lipopolysaccharide within the bacterial cell wall, resulting in the activation of an inflammatory cascade[37]. Immature intestinal cells exhibit an exaggerated inflammatory response when this system is activated[38].

Platelet-activating factor (PAF) is a phospholipid inflammatory mediator. When given experimentally to animals, it produces signs similar to those seen in infants with NEC and it has been shown to produce extensive intestinal injury in a piglet model of NEC[39]. Levels of PAF have been noted to be higher in preterm infants with NEC by a number of researchers and levels may be indicative of severity of the disease[40-42]. PAF increases in the blood and stools of infants affected by NEC and also in response to enteral feeding, which has been suggested as an important factor in the development of the disease[38]. PAF acetylhydrolase (PAF-AH), the enzyme that degrades PAF, is present at only low levels in newborn infants during the first few weeks of life, which may increase susceptibility to the damaging actions of PAF[43]. PAF-AH is present in breast milk, which is thought to be protective against NEC[44].

Increased levels of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6 have been seen in infants with NEC and may reflect severity of disease[42 45 46]. Conversely, levels of anti-inflammatory mediators such as IL-10 are low in preterm infants, indicating that there may be some loss of protection against inflammation in this group[47 48].

Many inflammatory and anti-inflammatory mechanisms are involved in the immune response to bacterial insult. It appears that immaturity of these immune systems contributes at different levels to render the preterm neonate susceptible to a variety of insults, which may then lead to a pathway culminating in the pathological signs of NEC. The pathogenesis of the disease is therefore likely to be related to a complex interplay between these mechanisms that has yet to be fully elucidated.

3.1.6 Genetic predisposition to NEC

Increasingly, genetic variation is being identified as a major factor in predisposition of individuals to disease states. A single change in the DNA code in a gene (single nucleotide polymorphism (SNP)) can alter the expression and function of that gene. Although this effect may be small, it may be sufficient to alter susceptibility to disease. There is a genetic component to preterm birth itself. Black women are more likely to deliver prematurely than white women; women who have had one preterm birth are more likely to deliver preterm again and recurrent preterm birth is seen in different members of the same family.

Researchers have therefore investigated genetic predisposition as a possible factor in the occurrence of NEC in neonates. Since regulation of the circulation and inflammatory responses are thought to be important in the development of NEC, genetic variation, relating to either of these systems, may make it more likely that an infant will develop the disease.

A recent study has investigated SNPs in the carbamoyl phosphate synthetase (CPS) 1 gene. CPS regulates production of L-arginine, which is a precursor of nitric oxide (NO). Deficiency in arginine may therefore be implicated in mucosal injury. This small case-control study showed that there was an increasing linear trend in incidence of NEC with the number of variant alleles in the CPS1 gene[49]. The retrospective nature of the study and the absence of data for other risk factors for the disease precluded further analysis to determine whether this genetic variation is an independent risk factor for NEC.

Genes involved in the inflammatory process have been more extensively investigated, although this type of research remains in its infancy. A recent study examined the influence of SNPs in the pattern recognition receptors TLR4, CD14 and caspase-recruitment domain 15 (CARD15), all of which are involved in binding of lipopolysaccharide. However, they found no association between genotype and prematurity, sepsis or NEC[50]. Nucleotide oligomerization domain 2 (NOD2) is another pattern recognition receptor that has been studied. CARD15/NOD2 is involved in the innate immune response and is expressed by intestinal cells. Mutations have been associated with sepsis in VLBW infants[51] and with Crohn's disease[52]. However, it does not appear to be involved in the pathogenesis of NEC[53]. A number of variations in cytokine encoding genes have been investigated, including TNFα, IL-6 and IL-10. Most studies have shown only modest, if any association between genetic variants and NEC and results have not been consistent between studies[54-56].

Although results of studies investigating the role of genetic variation in NEC have been, for the most part, negative, it is likely that this will continue as a rapidly expanding area of work in the future and may provide additional insight into the pathogenesis of this disease.

3.2 Clinical presentation and classification of NEC

Necrotising enterocolitis is certainly not a new disease entity. It is thought that it was probably first described by Genersich in 1891 who wrote of a 45 hour old premature baby who died within 24 hours following vomiting, abdominal distension and cyanosis[57]. However, further and more detailed descriptions first began to emerge in the 1960s. Mizrahi, in 1965, reported on 18 preterm neonates, born between 1953 and 1963, who developed a disease characterised by "necrotizing enteritis...with fibrinoid necrosis of the mucosa (involving) the lower ileum or the ascending and transverse colon or both, with frequent ulcerations, pseudomembranous inflammation, complicated at times by perforations and pneumatosis"[58]. Of the 18 infants reported by Mizrahi, some went on to develop a "shock-like" state and of the whole group, only two infants survived.

In 1975, Santulli *et al* reported their experience of the disease in 64 infants over a period of almost 20 years[57]. They concluded that there were different severities of the disease and that the incidence of the most severe manifestation of the disease or "fully developed" disease was "relatively low".

In 1978, Bell *et al* proposed a method of clinical staging based on clinical and radiological criteria (Table 3.1) to indicate the severity of disease in infants at the time of diagnosis of NEC[59]. This was in recognition of the fact that there appeared to be a very wide spectrum of disease, ranging from the mild form to a very fulminant and rapidly progressive disease. They derived this classification from a study involving 48 infants evaluated and treated for NEC in 1974 and 1975. These infants were born between 26 and 40 weeks of gestation (mean 33 weeks). All ten infants with Stage I disease survived and they therefore felt that it was more relevant to calculate the mortality for those with Stage II or Stage III disease; the mortality that they believed could be ascribed to NEC was 6/38 (15%). It was unclear whether those infants that were classified with Stage I disease had early NEC that responded completely and rapidly to treatment, or whether they had never, in fact, had NEC. In contrast, those with the most fulminant form of the disease responded poorly to treatment, whether medical or surgical. The authors concluded that NEC should be treated early and vigorously using medical therapies, reserving surgical intervention for those failing to respond or with complications such as gut perforation.

Clinicians and researchers have used Bell's staging criteria[59] (Table 3.1), since it was first proposed, to guide management, monitor the occurrence and standardise reporting of the condition. One recognised modification to the staging system by Walsh *et al*, published in 1986 (Table 3.2), particularly distinguished infants in whom bowel perforation complicated the disease[60]. This classification subdivides Bell's original categories and adds guidance on appropriate treatment for each stage.

Table 3.1: NEC staging system based upon historical, clinical and radiographic data[59]

Stage I	a.	Any one or more historical factors producing perinatal stress
(suspect)	b.	Systemic manifestations – temperature instability, lethargy, apnoea, bradycardia
	c.	Gastrointestinal manifestations – poor feeding, increasing pre-gavage residuals, emesis (may be bilious or test positive for occult blood), mild abdominal distension, occult blood may be present in stool (no fissure)
	d.	Abdominal radiographs show distension with mild ileus
Stage II	a.	Any one or more historical factors
(definite)	b.	Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding; marked abdominal distension
	c.	Abdominal radiographs show significant intestinal distension with ileus; small bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent "rigid" bowel loops, pneumatosis intestinalis, portal vein gas.
Stage III	a.	Any one or more historical factors
(advanced)	b.	Above signs and symptoms plus deterioration of vital signs, evidence of septic shock or marked gastrointestinal hemorrhage
	c.	Abdominal radiographs may show pneumoperitoneum in addition to others listed in IIc

Table 3.2: Modified Bell's staging criteria for neonatal NEC[60]

Stage	Systemic signs	Intestinal Signs	Radiologic signs
IA – Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pregavage residuals, mild abdominal distension, emesis, guaiac- positive stool	Normal or intestinal dilatation; mild ileus
IB – Suspected NEC	Same as above	Bright red blood from rectum	Same as above
IIA – Definite NEC, mildly ill	Same as above	Same as above plus diminished or absent bowel sounds with or without abdominal tenderness	Intestinal dilatation, ileus, pneumatosis intestinalis
IIB – Definite NEC, moderately ill	Above plus mild metabolic acidosis and mild thrombocytopenia	Above plus definite abdominal tenderness, with or without abdominal cellulites, or right lower quadrant mass, absent bowel sounds	Same as Stage IIB, definite ascites
IIIA – Advanced NEC, severely ill, bowel intact	Above plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation and neutropenia	Above plus signs of generalised peritonitis, marked tenderness and distension of abdomen	Same as IIB, plus definite ascites
IIIB – Advanced NEC, severely ill, bowel perforated	Same as Stage IIIA	Same as Stage IIIA	Same as Stage IIIA plus pneumoperitoneum

3.3 Incidence of NEC

NEC principally affects preterm infants and is one of the major causes of morbidity and mortality in this group worldwide. However, in studies where comparisons have been made, marked variations in incidence have been described between NNUs. When studies from different parts of the world are considered, there appears to be even more variation in occurrence of the disease between different countries.

The British Paediatric Surveillance Unit (BPSU) reported a study conducted in 1993-94[61]. This study was based on criteria defining two grades of disease. Grade I was defined as those cases having at least two of the following criteria: pneumatosis intestinalis; abdominal distension or an abdominal x-ray showing gaseous distension or frothy appearance of the bowel lumen, or both; bloody stool; lethargy, hypotonia, apnoeic episodes or a combination of these three features. Grade II was defined as cases having features of Grade I disease with, in addition, one or more of the following: abnormal bleeding in response to trauma or spontaneous bleeding; abdominal tenderness or rigidity; mucosal tissue in the stool; peripheral white cell count $<100 \times 10^9$ /l or free gas in abdomen or portal vein gas on x-ray. "Confirmed" cases were those where gas was present in the bowel wall or portal tract on abdominal x-ray or if a diagnosis of NEC was confirmed at surgery or post mortem examination. Using these definitions, 300 infants met the criteria for either Grade I or Grade II disease and of these, 185 had confirmed disease. Sixty-five percent of cases had birth weight <1500g. The estimated incidence of confirmed NEC reported by the BPSU in the UK, at this time, was 0.23 per 1000 live births and 2.1 per 1000 admissions to NNUs. The proportion of babies with confirmed NEC that died was 28%, with overall mortality being highest in the smallest babies. The study did not consider inter-unit variation in the incidence of disease.

Geffers *et al* reported the incidence of NEC as part of a prospective surveillance system for hospital acquired infection in very low birth weight (VLBW) babies in Germany, commenced in 2000[62]. NEC was included in this survey in view of the clustered nature of many cases, indicating a potential infective aetiology. They defined NEC as histopathological evidence of NEC or at least one characteristic radiographic abnormality, plus at least two of the following in the absence of any other explanation: vomiting, abdominal distention, residual gastric volumes prior to feeding, persistent microscopic or gross blood in stools. Characteristic radiological features included pneumoperitoneum,

pneumatosis intestinalis, and unchanging 'rigid' loops of small bowel. By the time of reporting in 2005, 52 NNUs had been surveyed for periods ranging from 1 to 5 years, with the inclusion of 8677 VLBW infants. They reported that 3.5% of babies developed NEC giving incidences of 1.1 per 1000 patient days in babies <1000g and 0.6 per 1000 patient days in larger babies. The addition of participating units at various stages during the period covered by the study may have introduced bias into the study results, depending on the size and type of units involved and the gestational ages and severity of illness of the babies for whom they provided care. Certainly, methodology of this kind would preclude any comparison of rates between German NNUs because of differences in the time over which data was collected. The proportion of 3.5% is somewhat lower than that quoted for a number of other developed Western countries and may be subject to question in the light of these factors, but this study provides the only available recent epidemiological data for NEC in Germany.

Data from neonatal intensive care units within the Canadian Neonatal Network in 1996-97 were obtained to examine variation in clinical practice and outcomes, including NEC[63]. Trained research assistants collected these data prospectively, from the medical records of mothers and babies, as part of the larger study involving 19,507 infants admitted to NNUs in Canada. NEC was defined for the purposes of this study according to Bell's criteria for Stage II disease or greater. It was further classified as "medical" disease (clinical signs and symptoms of disease, with pneumatosis seen on X-ray) or "surgical" disease, requiring histological evidence of NEC from a specimen taken at surgical intervention. The incidence of NEC in 3,692 very low birth weight (VLBW) babies (i.e. birth weight <1500g) was 6.6%, again with the highest rates in the smallest babies[64]. The crude incidence of NEC in this cohort ranged from 0% to 13.3%, with one NNU reporting no NEC during the period of study. The authors do not report on mortality. Differences in NEC rates between units were not statistically significant before or after adjustment for baseline population risks and illness severity. Data collection methods in this study appear to have been robust but it is interesting to note the 0% incidence in one NNU with 93 admissions of VLBW babies. Reasons for this might include either under-reporting of the disease or a true difference in incidence, perhaps generated by differences in clinical practice or population, or a chance finding.

Data from the United States of America (USA) have shown a similar incidence of NEC to the Canadian study. In 1991, Uauy *et al* reported the incidence of NEC in 8 NNUs belonging to the National Institute of Child Health and Development (NICHD)[7]. They studied 2681

infants weighing <1500g born during an 18-month period between 1998 and 1999 and classified NEC according to the modified Bell's staging. In their analysis, "suspected NEC" was used to describe stages IA and IB and "proven NEC" was used to describe stage IIA and more advanced stages; they used the term "perforated NEC" to describe stage IIIB. One of the study objectives was to examine variation in rates of the disease between centres. The overall prevalence of proven NEC was 10.1%, with a further 17.2% of infants falling into the category of suspected NEC. Mortality in this group for Stage III NEC was 50%. Rates of NEC differed between centres from 3.9% to 22.4%. The authors speculated that this might relate to differences in clinical practice rather than population differences, but were unable to show this conclusively due to limited numbers of subjects.

A further NICHD study, conducted between 1998 and 2001, studied 11,072 infants with birth weight below 1500g surviving for 12 hours or more after birth in 19 units[65]. Of these infants, 7.1% went on to develop NEC overall, with the figure rising to 11.4% in babies with birth weight of ≤ 750g. Modified Bell's staging criteria were used for classification of disease in this study. Stages IA and IB were defined as "suspected" NEC. Stages IIA, IIB or IIA were defined as "proven, no surgery" and Stage IIB disease was defined as "proven, surgery". In this study, the incidence of NEC varied from 4.26-11.25% ($p<0.0001$) between centres. Mortality was not discussed.

In 2000, also in the USA, Holman *et al* estimated rates of NEC as defined by the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) code 777.5 (necrotizing enterocolitis in fetus or newborn)[66]. They obtained data from hospital discharge records from the Kids' Inpatient Database produced for the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research. Since data were anonymised, the analysis was based on hospital admission episodes and final discharge/death data rather than infants, to avoid bias due to inter-hospital transfers and associated duplicate counting of infants. This study revealed that approximately 1 per 1000 live births was given a diagnosis of NEC during their neonatal hospitalisation. As in previously described studies, the largest proportion of affected babies was among those of very low birth weight. Mortality rates were high (15.2%). They also examined rates of NEC according to geographical regions, but observed no statistically significant differences.

In 2002 the Vermont Oxford Network (VON), comprised of 331 NNUs in North America and 31 units in a total of 17 other countries, reported data from 1991-1999 for the 362

participating NNUs[67]. Only 39 of the participating units, however, were involved in data collection for the full 9-year period. Rates of NEC remained relatively steady among infants <1500g throughout the whole 9-year period, ranging from 6.0% to 7.1% when considering all participating units and from 6.2-8.4% when considering only those units that participated for the whole time. Although these estimates do not represent population-based data, the VON database collects data from widely varying and geographically diverse areas in developed countries and is likely to be representative of clinical practice in the USA and other Western countries and these results are in line with other large sequential studies in the USA.

Trends in rates of NEC have also been explored in Australia. Luig *et al* reported a retrospective population-based study utilising prospectively collected data from the New South Wales Neonatal Intensive Care Unit Study database[68 69]. They examined data from three epochs: 1986-1987, 1992-1993 and 1998-1999. Units joining the group at any point included in this total time period were excluded to ensure integrity of data. NEC was defined as clinically suspected NEC plus at least one of the following: abdominal wall cellulitis and palpable abdominal mass, pneumatosis intestinalis, portal vein gas, persistence of a rigid dilated bowel loop seen on serial x-rays, or diagnosis at surgery or post mortem examination. In contrast to the studies from the USA, this Australian study showed decreasing incidence of proven NEC across the three epochs (9%, 10% and 5% respectively for the three periods ($p<0.001$)), in spite of significantly increasing numbers of surviving ELBW infants. However, this did not translate into a reduction either in the numbers requiring surgery or in overall mortality rates for the condition. The authors were unable to show any parallel trends with respect to changes in clinical practice or population that might account for this finding.

3.3.1 Limitations in reporting of the incidence of NEC

A major challenge in monitoring the incidence of NEC lies in the inconsistency of the definitions used by different research groups, in spite of the availability of the staging system introduced by Bell[59] and since modified. It is clear from the above studies that definitions are poorly standardised between studies. Although in most research the criteria used are based on those included in either the original or the modified staging, they differ in detail, making interpretation of multiple studies difficult and combination of results inappropriate. Some

groups, for example the BPSU in their report, have chosen to devise a separate and different classification of disease for the purpose of their study[61].

With increasing experience in the care of VLBW and extremely low birth weight (ELBW) infants, significant limitations of Bell's staging system have been recognised. Firstly, there is a lack of specificity in the classification of stage I, or "suspected" NEC. Systemic diseases of any kind, and in particular those of infectious aetiology, may produce any or all of the manifestations that Bell describes. Temperature instability, episodes of apnoea and episodes of bradycardia are frequently seen with systemic sepsis and "localising" features such as abdominal distension and increased residual volumes on gastric aspiration can often more appropriately be attributed to intestinal ileus secondary to severe systemic illness. This imprecision creates the potential for misclassification of disease with the likelihood of overestimation of the occurrence of NEC. This has led most researchers to consider only a diagnosis of Stage II or III NEC as significant or indicative of proven disease. Where data collection occurs prospectively, this is probably a reasonable approach, but in retrospective studies or those for which the attribution of disease status relies upon coding of diagnosis at discharge, the accuracy of data collection is less predictable, being dependent on retrospective interpretation of the clinical condition. In addition, restriction of investigations to confirmed Stage II or III NEC does not allow consideration of the impact of Stage I disease on treatment and outcome of infants.

Secondly, a further limitation has recently led researchers and clinicians to question the appropriateness of using Bell's staging of NEC in the current and more "modern" climate of neonatal medicine[26]. With advancing knowledge and skills, the survival of extremely preterm and ELBW babies has increased significantly. With this increasing survival, changes in patterns of disease have been noted and a condition that may previously have been attributed to NEC, according to Bell's criteria, has emerged as an entirely separate entity. Spontaneous intestinal perforation (SIP) was first described in detail in a case series by Aschner *et al* in 1988[70]. In SIP, there is perforation of the bowel wall, usually in the ileum, but without pathological features consistent with NEC and generally carrying a better prognosis. SIP has probably occurred for a long time, but the incidence appears to have increased substantially in recent years, probably at least in part due to the more widespread use of drugs such as steroids and non-steroidal anti-inflammatory drugs. Lack of recognition of this condition and therefore a tendency to ascribe a diagnosis of NEC to any bowel

perforation in an immature infant may also feature as an important source of error in the challenging task of determining the incidence of NEC in the preterm population.

Differences in reporting methods may also contribute to difficulties associated with collection of accurate data on NEC. The BPSU study relied on reporting of cases by clinicians to a central body. Since under-reporting is common in surveys of this kind, it is possible that their results may represent an underestimate of the true impact of the disease in the UK. Accuracy in retrospective data collection is challenging. Routine prospective population-based collection of details of diagnosis is probably the most robust means of obtaining accurate and complete data, but for a condition such as NEC which, although extremely important clinically, is a rare outcome, very large populations will be required to produce data over a substantial time span to allow meaningful rates to be obtained. This is particularly so with NEC, since disease rates appear to fluctuate significantly with time and location. The large databases in the USA such as the NICHD and VON databases are probably best placed to be able to provide such data. However, although these are large populations, given the variation between different countries, their data will not necessarily be generalisable to other areas of the world and the confounding introduced by cultural and economic differences may preclude comparison between countries.

Nevertheless, despite inconsistencies in definition and potential for the introduction of error, most studies support the conclusion that NEC is an important disease with consistently high rates of morbidity and mortality and one in which changing trends in neonatal care have failed to make a significant impact either in reducing incidence or improving outcomes.

3.4 Risk factors associated with the development of NEC

Given the high rates of morbidity and mortality associated with NEC, it is not surprising that much effort has been directed towards attempts to identify causal factors in this condition and towards ways of preventing or reducing the burden of neonatal disease. In spite of this, the aetiology of NEC has remained obscure and there are likely to be multiple contributing factors involved. A host of risk factors, pertaining both to the babies' clinical condition and to neonatal interventions, has been proposed as a result of multiple observational studies.

There appear to be two distinct patterns in the occurrence of NEC. Clusters of cases or "outbreaks" have been observed leading researchers to explore in detail the concept of an infective cause for the disease. However, this by no means accounts for all cases and many seem to have a sporadic pattern. The majority of epidemiological studies have chosen to focus on the identification of clinical risk factors that are commonly associated with NEC. Although all studies agree that the most consistent factor associated with NEC is prematurity, this alone does not account for all cases. Around 10% of cases of NEC occur in term born infants although the risk of disease is far lower than in the preterm and may reflect different pathogenetic mechanisms. A discussion of NEC in term infants is beyond the scope of this thesis.

The age at which preterm neonates develop NEC is extremely variable, with a tendency towards somewhat later onset in the most preterm babies compared with larger and more mature preterm neonates. This variability in the time of onset suggests that it is not only predisposing conditions present at or soon after birth, but also later environmental factors or clinical interventions that may promote development of disease. Several factors have been identified that may represent "iatrogenic" aspects contributing to the disease process.

The evidence for each of the risk factors that are considered potentially important in preterm and VLBW infants will be considered in detail in the following sections.

3.4.1 Gestational age and birth weight

More than 90% of cases of NEC occur in preterm infants. Studies have consistently shown that this is the most important risk factor. There is a strong relationship between birth weight and gestational age and most researchers have chosen to analyse their study results by birth weight. This may lead to inclusion of some babies that are small for their gestational age. This and the fact that many studies were conducted some years ago when survival in babies of the lowest gestational age was less common, means that many included babies are more mature than those on whom the greatest concern now focuses.

A number of studies have suggested that not only is prematurity an important factor in the development of NEC, but that it may be the only significant risk factor. Although these studies examined the influence of other factors that had previously been implicated in the

pathogenesis of NEC, they were unable to confirm relationships with any other risk factors other than gestation and/or birth weight. Stoll *et al* used a case control design to study 35 babies with NEC and 98 controls[71]. Babies were matched for birth weight and the mean gestational age was 31 weeks in both groups. This study found that NEC was commoner in the smallest, least mature and sickest babies. The overall incidence in the group was 6 per 1000 live births, rising to 66 per 1000 live births in infants with birth weight of <1500g. The age at onset of the disease was inversely proportional to gestational age at birth. They suggested that prematurity was the greatest risk factor and hypothesised that smaller babies who have been most unwell develop NEC later possibly due to ongoing insults to the maturing gut on recovery from acute illness after birth. In 1987, De Curtis *et al* performed a study of 27 cases and 54 weight-matched controls[72]. Their results confirmed these findings and they were unable to show a significant association with any other risk factors. Both studies included mature infants and had limited power to detect differences.

Kanto and Lui conducted similar case control studies but included only low birth weight preterm infants[73 74]. They too found that the occurrence of NEC was inversely related to birth weight and gestational age and were unable to identify other risk factors. Lui *et al* also noted an inverse relationship between gestational age and the time of presentation with the disease.

Guthrie *et al* retrospectively analysed data from 98 NNUs within the Pediatrix Medical Group Inc. across the USA[75]. Included infants were inborn babies between 23 and 34 weeks of gestation. Using logistic regression, they analysed prospectively identified risk factors for NEC by univariate analysis and found a number to be significant. However, when included in multivariate analysis adjusted for birth weight, many lost significance and they concluded that birth weight was the most important factor. They also examined cases according to whether they were treated medically or surgically and showed that surgically treated babies were more likely to be of lower birth weight and gestational age than conservatively treated infants. Sharma later showed that the clinical presentation of NEC and management by surgeons also differ with gestational age[76].

Palmer examined the confounding effects of both birth weight and gestational age. They found these to be similar and chose to report their analysis by birth weight[4], dividing their study groups according to birth weight above or below 1500g. Interestingly, their results suggested that risk factors for NEC might vary with gestational age; smaller babies with events or conditions leading to prolonged hypoxia were at greater risk, whereas in larger

babies, the most common risk factor was hypoxia at birth. Beeby studied babies born at <36 weeks of gestation in a case control study of 74 infants matched for gestational age and also found differences between more and less mature infants[77]. In infants born between 25 and 29 weeks of gestation (n=35) they were unable to identify any risk factors other than prematurity, suggesting that this group are at risk of NEC purely by virtue of their gestation at birth. In contrast, more mature infants (n=8) all had identifiable predisposing factors of asphyxia or intrauterine growth restriction. Luig and Lui looked at a group (n=178) of even less mature babies with NEC[69]. They showed that incidence of and mortality from NEC both increased with lower gestational age. The proportion of the disease in babies of 24-27 weeks' gestation was 6.6%, falling to 2.6% in babies born between 28 and 31 weeks of gestation. In the more mature preterm group, the only risk factor identified was surgical treatment of patent ductus arteriosus, whereas the less mature infants were more likely to have risk factors associated with NEC. However, these risk factors were common in all the smaller infants.

Whilst all studies have considered gestational age and/or low birth weight as a major risk factor for NEC, results have been conflicting regarding the contribution of other risk factors in development of the disease in association with prematurity. Some have suggested that other risk factors cannot be identified. If gestational age were the only contributing factor in NEC, it might be expected that the incidence of the disease would be rising in line with increasing survival of extremely preterm infants. However, Luig and Lui showed that, in their cohort of infants born at 24-28 weeks of gestation, the incidence of NEC decreased steadily over time, despite increasing survival of high-risk infants or low gestational age[68 69]. There were many potential risk factors that were not considered in this study and it seems more likely that declines in the incidence of NEC were related to changes or advances in care over the study period. Overall, the evidence suggests that prematurity is the most consistent and important risk factor, but that there may be many other contributing factors necessary for the development of NEC and influencing the severity of the disease. Since NEC is a relatively rare outcome and the presence of multiple and variable risk factors is common in most sick preterm babies, the true influence of gestational age *per se* is almost impossible to determine with certainty and this probably accounts for the conflicting results seen in the studies.

3.4.2 Intrauterine growth restriction

3.4.2.1 Assessment of intrauterine growth at birth

In the first trimester and early part of the second trimester of pregnancy, foetal growth is characterised mainly by increasing cell numbers. During the later stages, this changes and the fetus enlarges primarily by increase in cell size. By the time of the last trimester fat, muscle and connective tissues are laid down. By far the largest proportion of weight gain takes place during the latter half of pregnancy. Disturbance or slowing of this process can occur for a number of reasons such as placental insufficiency or maternal illness, leading to the birth of a baby that is smaller than would be expected at full term, when taking into account the normal range of weights for male and female infants.

Intrauterine growth restriction (IUGR), previously known as intrauterine growth retardation, has been defined in a number of ways, with the commonest definition being that of birth weight below the tenth percentile on the growth chart. Others have taken it as birth weight falling less than two standard deviations below the mean; this corresponds approximately to the level of the third percentile. For the purposes of this study, the first of these definitions was used. The term "growth restriction" is frequently used interchangeably with the term "small for gestational age". However, this is not strictly correct, since the latter group may contain infants who are constitutionally small because they have small parents. Other infants may be small because of their ethnic origin. Many of these babies for whom it is "normal" to be small may fall below the tenth centile on the growth chart. However, such babies are at no greater risk either during pregnancy or during the perinatal period than larger normally grown infants. This is in contrast to those infants for whom their small size represents the result of an intrauterine insult and a significantly increased risk of early morbidity and mortality. The limitations of growth reference charts can be clearly appreciated, but it would not be feasible to take account of every eventuality when devising such a reference source.

Measurement of intrauterine growth and the implications of different rates of growth became a topic of interest in the 1960s[78] and it was noted that babies with poor intrauterine growth were at high risk of having congenital anomalies[79 80]. An increased mortality rate in these infants was confirmed in other cohorts[81 82]. This early work focused mainly on mortality in infants born at term. Later studies investigated morbidity within this group.

3.4.2.2 Abnormal antenatal umbilical artery Doppler studies and NEC

Prenatally, studies of Doppler waveform velocities in the umbilical artery are commonly used as an obstetric measure of fetal wellbeing in high-risk pregnancies. These studies may show varying degrees of increased placental vascular resistance, ranging from reduced end diastolic flow in the umbilical artery to absent (AEDF) or even reversed end diastolic flow (REDF), which have a strong association with fetal compromise and chronic hypoxia. Foetuses affected by such placental insufficiency usually display poor *in utero* growth. The finding of AEDF or REDF on antenatal Doppler studies will prompt most obstetricians to intervene and deliver the preterm baby in view of the high risk of intrauterine demise. Depending on the stage of gestation, lesser degrees of compromise may be monitored for a period of time, especially if it is thought that risks of prematurity are greater than the risk of intrauterine death in the growth restricted fetus. Although improved obstetric services have led to more frequent monitoring of antenatal umbilical Doppler velocities in high-risk pregnancies, these studies are not performed in all pregnancies, and in some centres this investigation is not available at all. Therefore this information is not currently available for all preterm deliveries, even where IUGR may have been identified on fetal measurement.

Chronic hypoxia associated with poor placental perfusion results in a redistribution of blood flow in the fetus to preserve cerebral circulation. This often leads to asymmetrical growth in the affected fetus with the head circumference being proportionately greater than expected for the birth weight, so-called "brain sparing". Hackett *et al,* in a retrospective review of data from Doppler studies in growth restricted fetuses, showed that this preservation of cerebral perfusion resulted in decreased blood flow in the descending aorta[83]. Aortic blood flow velocity was significantly more severely impaired with increasing growth restriction. Kempley *et al*, in 1991, investigated the hypothesis that these prenatal haemodynamic disturbances persist into the postnatal period by studying superior mesenteric artery (SMA) and coeliac axis blood flow velocity in infants with antenatally diagnosed growth restriction[84]. Compared with control infants matched for weight and gestational age at birth, these infants showed reduced abdominal blood flow velocities, but no difference in cerebral blood flow velocities, suggesting that this is the case. Differences were most marked in infants with antenatal AEDF and only a slow recovery was seen during the first seven days of postnatal life. A later study by Maruyama showed similar results[85].

A number of studies[86-88] have shown an association between IUGR and the postnatal development of NEC in preterm infants, while others have failed to demonstrate this. Garite

et al, by retrospective analysis of a large dataset including more than 1000 growth restricted neonates, showed an increased risk of NEC in infants born at 25-32 weeks of gestation[88]. Gilbert *et al*, also in a retrospective review showed a significant increase in NEC that was confined to infants of more than 34 weeks of gestation[87]. However, this study only included infants who survived to one year of age, so it is possible that this will have overlooked some immature infants with NEC who may have died from this or other complications of extreme prematurity. Simchen *et al*, in a smaller retrospective study, found a trend towards increased NEC in growth-restricted infants[86]. In contrast, Pena *et al* did not show any increase in NEC related to IUGR[89].

Further studies have looked more closely at the relationship between abnormal antenatal Doppler studies and NEC. Again results have proved conflicting. Adiotomre *et al,* in a retrospective review of 60 infants did not find any increased association between NEC and AEDF[90]. Hackett *et al* analysed the history and neonatal outcome where Doppler studies were carried out in pregnancies and birth weight was below the 10th centile[83] . A greater proportion of babies where there had been AEDF developed NEC. Malcolm *et al* in a case control study of 25 high-risk pregnancies with absent or reversed end diastolic umbilical artery flow showed a similar relationship and concluded that this was an independent risk factor for NEC[91]. Other retrospective studies by Karsdorp, Kirsten, Soregaroli and Müller-Egloff found no statistically significant difference between groups with abnormal and normal Doppler studies[92-95]. Many of these studies have included small numbers of infants and therefore lack power to detect a real difference between the study groups. A meta-analysis[96] of 14 studies examining the risk of NEC in infants where Doppler studies have been abnormal showed an increased risk with absent or reversed end diastolic flow in the umbilical artery or aorta. Since this meta-analysis, two further studies have been published. Kamoji *et al* included 206 infants in a retrospective analysis of infants with NEC in whom information about antenatal Doppler studies was available[97]. This showed a highly significant association, after adjustment for gestation at birth and birth weight between abnormal Doppler studies and infants with either suspected or definite NEC. There was a twofold increase in stage II or III (confirmed) NEC in those with abnormal Dopplers, but this was not statistically significant. The most recent study to address this question was a prospective multicentre study in which 404 fetuses were assessed antenatally with umbilical artery Doppler studies[98]. Thirty-nine neonates developed NEC. The authors were unable to demonstrate any correlation between worsening antenatal Doppler study results and the development of NEC, which might be expected if the relationship were causal.

One common thread running through many of the studies of antenatal Dopplers and NEC is that, because obstetricians usually deliver infants when fetal compromise becomes severe, infants with absent or reversed end diastolic flow tend to be more preterm and of lower birth weight than their growth-restricted counterparts with normal Doppler studies. It is therefore possible that the higher rates of NEC in these babies may be related to the recognised risk factors of gestation and birth weight.

3.4.3 Enteral feeding

The observation that more than 90% of infants developing NEC have received some form of enteral feeding[3] has led to scrutiny of feeding practices in an attempt to investigate whether a causal relationship exists. A review of the available literature pertaining to enteral feeding in preterm infants reveals substantial changes in practice over time for virtually every aspect of feeding. Changes have occurred gradually in response both to mounting evidence from research and to changes in the population of babies cared for in the newborn period with increasing survival of smaller and more immature infants.

3.4.3.1 Withholding of enteral feeds

When neonatal care of premature babies was in its infancy, the practice of allowing a period of starvation was common. This arose, not from concerns about the development of gastrointestinal disease, but from fears of respiratory compromise due to aspiration of milk[99]. In view of the observed irritant effect of aspirated milk, the usual practice, on introduction of enteral feeds, was for water or glucose to be administered orally or via nasogastric tube, depending on the maturity of the infant. Bauman questioned this indication for the starvation of infants in 1960[100], randomly allocating infants admitted to the NNU to receive sterile dextrose-saline solution nasogastrically either before 6 hours of age or after 36 hours. He was, however, unable to demonstrate a clear beneficial effect on respiratory morbidity in either group. A further study by Wennberg *et al*[101] showed that early feeding resulted in less jaundice and weight loss and that administration of a glucose solution led to improved glucose levels compared with sterile water feeds. Other concerns developed about the possible effect of a prolonged period of nutrient starvation on brain growth and development. As nasogastric feeding and other nursing techniques improved, anxieties about the likelihood of aspiration of milk lessened and attention turned to whether milk feeds could be given safely within the first hours of life. Smallpeice and Davies demonstrated earlier regain of

birth weight, reduced hypoglycaemia and hyperbilirubinaemia in 111 infants fed undiluted human breast milk[102]. Wu confirmed these findings in infants fed in the first hours of life with formula milk[103].

Most of these studies were undertaken in babies of >1500g and >34 weeks of gestation in an era when it was said that babies with a birth weight of <1000g "almost invariably die"[102]. With rapidly improving methods of neonatal intensive care in subsequent years leading to survival of the smallest preterm babies and increasing documentation of cases of NEC[57 58], the type of feeds to be given, the timing and methods of introducing enteral feeds once more became controversial.

3.4.3.2 Type of feed

(a) Breast milk or formula milk?

For infants born at or near term, there is overwhelming evidence that breast milk has important benefits, both in the long and short term. These relate to the immuno-protective effects of breast milk. Immunological components of breast milk are lactoferrin, secretory IgA and lysozyme, which are thought to protect against infection. Breast-feeding in this group is associated with reduction in gastrointestinal illness[104] and infection[105], protection against later atopic conditions such as asthma and eczema[106 107] and beneficial effects on cognitive development[108]. Long-term developmental effects are thought to be related to long chain polyunsaturated fatty acids, which are components of human milk, but not of cow's milk.

Studies comparing feeding with maternal breast milk or preterm formula milk in preterm and LBW babies have been fewer and none are randomised [109]. Follow-up of a large group of infants participating in a trial of glutamine supplementation provided an opportunity for Vohr *et al* to assess developmental outcomes in relation to early feeding[110]. Children receiving any, as opposed to no breast milk scored more highly on Bayley Scales of Infant Development (BSID) at 18 months of age. Takana *et al*, in Japan, recently studied the relationship between breast-feeding and cognitive function in a small group of preterm infants, of whom 10 received >80% breast milk in the first 4 weeks of life and 8 received <80% breast milk[111]. They found a significant difference at 5 years of age in head circumference and some cognitive skills in those receiving more breast milk. However, the study included only small numbers and did not consider confounding factors, such as maternal education, postnatal environment and parenting behaviours, all of which may

influence child development. Although these studies are observational rather than randomised, the results are supportive of the hypothesis that similar effects to those in mature infants also exist in preterm infants. However, Furman *et al* were unable to demonstrate an effect on developmental outcome in 98 infants due to breast milk after adjusting for confounding factors[112].

Most studies in preterm and LBW infants have concentrated on short-term outcomes including NEC and neonatal infection. Although NEC undoubtedly occurs in infants fed exclusively on breast milk, observational studies have indicated that breast milk may confer some protection against the disease. Lucas and Cole, in 1990, used two parallel, randomised studies involving 926 infants to assess the role of different types of milk in the development of NEC[113]. Infants in three centres received preterm formula or pooled donor breast milk and groups were stratified according to whether maternal breast milk was also provided. This allowed comparison of donor milk and preterm formula as sole nutrition or as supplements to maternal breast milk. In a further two centres, infants were similarly randomised to receive either preterm or term formula in addition to breast milk, if provided. They observed no difference in the incidence of NEC between infants given pooled donor breast milk, or maternal breast milk, but there was significantly more confirmed NEC seen in the formula milk groups, with these differences remaining significant after adjustment for confounding factors. The risk of disease was also higher in exclusively formula-fed infants compared with those fed some breast milk in addition to formula. Benefits increased with decreasing gestational age[114]. Lucas *et al* later demonstrated benefits in terms of later development at 18 months[115], assessed using BSID and increased verbal intelligence quotient scores in boys at 7-8 years of age[116].

A number of more recent observational studies have also reported decreased rates of NEC and/or sepsis with breast milk feeds compared with formula. Furman *et al* prospectively studied 119 VLBW infants and showed significantly lower rates of infection in the first month of life in infants who received >50ml/kg per day of maternal milk compared with those receiving less[117]. In this study, there was no effect on incidence of NEC, but the sample size would have been inadequate to detect a difference in this. Whilst birth weight, ethnicity and gender were considered in analysis, severity of illness was not taken into account. Schanler *et al* studied babies of <30 weeks of gestation whose mothers intended to breast-feed[118]. Infants were randomly allocated to supplementation with donor milk or preterm formula if maternal milk was insufficient; 29% received only maternal breast milk and 21%

changed from donor breast milk to preterm formula because of poor weight gain. Intention to treat analysis showed a significant difference between those who only received maternal milk and the other groups, with maternal milk-fed infants having fewer episodes of infection and/or NEC and shorter hospital stay. No such differences were seen between the donor milk and formula groups, indicating that maternal milk may confer benefits over donor breast milk. Meinzen-Derr *et al* have recently analysed further data from 1272 infants involved in their randomised trial of glutamine supplementation to investigate the effects of human milk on the combined outcome of NEC and death[119]. In this group, after adjusting for multiple confounding factors, increases in the cumulative amount of human milk fed were associated with decreasing risk of NEC or death, suggesting a dose-response relationship.

Comparison of the effects of breast milk and formula are fraught with difficulties. Feeding method is highly dependent on maternal wishes and supply of maternal breast milk and these factors cannot be manipulated or controlled. There are many other important factors that may be associated both with feeding practices and with outcomes. Some of these are dependent on the clinical condition of the infant, some relate to differing opinion and practice among clinicians and others to maternal characteristics, such as socioeconomic status and education level, which are known to influence breast-feeding rates. Since NEC is a relatively rare disease, large numbers are likely to be necessary to demonstrate differences between groups of infants, even with rigorous controlling for confounding factors. The numbers of babies at highest risk of NEC are small and even studies of national data may be inadequate to provide definitive results. In addition, geographical variation and waxing and waning in incidence of the disease further complicate the issue. Another difficulty lies in achieving results from "pure" groups, since the majority of infants receive a combination of breast milk and formula, due to problems encountered by many mothers in expressing sufficient breast milk for the nutritional and volume requirements of their babies, particularly in the first few days of life. Current recommendations[120] favour breast milk as the most appropriate form of enteral feeding for preterm infants and in view of the known immunological benefits it is unlikely that randomised trials will ever be conducted.

(b) Maternal breast milk or donor breast milk?

A substantial number of mothers of preterm infants either do not wish, or are not able to provide breast milk. The clear benefits of breast milk have led to the provision of third party donated breast milk by human breast milk banks[121]. Currently, there are 17 established breast milk banking facilities in the UK, 11 in the USA, and 1 in Canada, with further banks under

development. Milk distributed by such banks is pooled donated milk usually originating from mothers of term infants. Differences in content of term milk compared with preterm milk may be important when considering the value of donated breast milk for preterm infants. Milk constituents may also be affected by the degree of prematurity. Concern about transmission of infection through breast milk mandates processing of donated milk using pasteurisation. However, pasteurisation, whilst eliminating the risk of transmission of bacteria and viruses such as the Human Immunodeficiency Virus (HIV), also affects some of the nutritional and immunological components of the milk.

Long chain polyunsaturated fatty acids (LCPUFAs), in particular docosahexaenoic acid (DHA), appear to be important for early cognitive and visual development [122 123]. Humans cannot synthesise these fatty acids and therefore the fetus depends on placental transfer during the final trimester of pregnancy, which is a period of rapid growth, brain development and deposition of adipose tissue. For the extremely preterm infant, LCPUFAs must be provided in enteral feeds. A systematic review by Bokor *et al* examined differences in fatty acid content between term and preterm human milk[124]. This review identified five longitudinal studies comparing content of milk from mothers delivering at 25 to 30 weeks of gestation or at >37 weeks[125-129]. Three of these studies showed higher levels either of DHA or its intermediaries in preterm human milk compared with term milk[126 128 129]. This is most likely to be explained by the fact that mothers delivering prematurely have accumulated stores of LCPUFAs, but placental transfer has not occurred. The authors speculate that adaptive mechanisms, designed to provide for the *ex utero* needs of a preterm infant, may play a part, but this is an untested hypothesis. These results suggest that maternal milk, rather than donated breast milk may confer benefits for the preterm baby.

Differences in levels of immunoglobulin have been shown in several studies. Barros *et al* observed higher levels of IgA, IgG and IgM in colostrum collected from 17 mothers of preterm babies compared with that of 18 delivering at term although they noted similar profiles in milk from mothers of full term growth restricted infants[130].

Lepage *et al* showed differences in calorie, nitrogen and fatty acid content of milk produced by mothers at 26-31 weeks of gestation compared with later preterm gestations[131]. Anderson *et al* also showed higher calorific and protein content in preterm compared with term milk, based on 24 hours of expressed breast milk (EBM)[132]. Gross *et al,* in a small study including 26 mothers, confirmed higher protein levels in preterm expressed milk, compared with EBM

from mothers delivering at term, but showed no difference in calorie content between the groups[133]. Conflicting results may be due to variability in milk composition between individuals, differing gestational ages and/or small numbers in the studies, but there is a paucity of further work and large studies in this area.

Schanler directly compared the composition of milk from mothers who had delivered preterm with pooled donated breast milk [134]. This study showed significantly higher nitrogen content initially in preterm mothers' milk, with gradually decreasing levels that approached those of the donated milk after two weeks. Mean calcium content was also higher in preterm mothers' milk. However, the author was unable to conclude from this work whether these findings would translate into growth-related benefits for the premature infant. A recent study examined calorie content of 415 samples of donor breast milk from 273 mothers and showed this to be 19kcal/oz, compared with an accepted average value of 20kcal/oz for term breast milk[135]. In view of the increased metabolic demands of preterm babies, the authors suggest that this may not be sufficient to meet these demands without the use of breast milk fortifier.

The process of pasteurisation is known to affect the immunological components of breast milk. Koenig *et al* analysed samples of raw and pasteurised colostrum from 101 mothers delivering at different gestations, both preterm and term[136]. In this study, protein, lysozyme, IgA and IgG concentrations were all significantly reduced by pasteurisation. However, the authors concluded that appreciable amounts of protein and IgA were retained, particularly in preterm milk, that might reasonably be expected to provide some benefit to the preterm baby though this is likely to be less than mother's own untreated milk.

Four randomised trials[113 137-139], all conducted before 1985, have considered the role of donor breast milk feeding compared with formula milk in the prevention of NEC. None found statistically different rates of NEC between the groups. A more recent meta-analysis of results of these studies revealed a lower incidence in the groups fed with donor milk[140]. However, this should be interpreted with caution in view of differences in the population and management of preterm infants at the time of these studies compared with current neonatal care. A further single centre study reported in 2005 by Schanler *et al* included infants born at 23 to 29 weeks of gestation. Infants were randomised to receive either donor milk (n=81) or preterm formula (n=92) if supplementation of mother's own milk was required[118]. In this study, 21% of the infants given donor milk were changed to preterm formula supplementation because of poor weight gain. NEC occurred in 6% and 11% of babies

respectively for the donor and formula milk groups, which did not represent a statistically significant difference. The authors concluded that the study did not provide evidence of any short-term advantage of donor milk over preterm formula for extremely preterm infants, but that further larger studies examining long-term outcomes may be warranted.

Differences in constituents between maternal breast milk and pooled donated milk may have an important impact on health and development, but randomised comparison between exclusive feeding with mother's own milk versus exclusive feeding with donated breast milk would not be ethically acceptable. At the present time, third party donated breast milk is not universally available and its use in the UK is determined by policies of individual NNUs, additional cost implications associated with provision of a milk banking service, accessibility of milk banking facilities, supply of donor milk and acceptability of the process to mothers of preterm infants.

(c) Term or preterm formula?

In circumstances where mothers of preterm babies cannot, or are unwilling to express breast milk and donated milk is not available, an alternative artificial feed must be used. The composition of term formula milk is based on the composition of human breast milk produced by mothers of term infants, whereas preterm formula is specifically designed to meet the additional nutrition and growth needs of a preterm infant. Preterm formula products contain, in particular, higher amounts of protein and carbohydrate than term formulas. The lactose content of preterm milks is reduced to avoid the risk of lactose intolerance by the immature gut. The calorie content of preterm formula is around 80kcal/100ml, compared with term formulas in which the energy content is around 60-70 kcal/100ml.

Infants given preterm formula are more able to achieve rates of growth comparable to those *in utero*[141 142]. There have been few trials comparing the effects of feeding preterm or term formula to preterm infants. Lucas *et al* performed two parallel, randomised trials to examine the effects of early feeding on long term outcomes[143]. In the first, they randomised preterm infants to receive either donor breast milk or preterm formula and in the second, either term or preterm formulas either as a supplement to breast milk (n=264) or sole diet (n=160). This was continued until the infants reached a weight of 2000g and thereafter the parents and clinicians determined feeding. Infants in the second trial who received preterm formula had better gain in weight and head circumference[144]. At 18-month follow-up, those who had been fed with preterm formula had significantly higher scores for both mental and motor

development and developmental impairment was higher in the term formula group[145]. The same group of infants was later followed up at the age of 7.5 to 8 years to assess long-term growth and development. At this stage, no effect of the early diet on growth was found, suggesting that improvement in early nutrition is not reflected in improved long-term growth parameters[146]. However, particularly in boys, improved cognitive outcomes were seen in the group fed preterm formula and the incidence of cerebral palsy was less in this group[116].

Despite these apparent advantages of preterm formula over term formula in the absence of expressed milk, concern exists over whether it is the optimal milk with which to feed preterm neonates during the first weeks of life. Jadcherla and Berseth noted poor tolerance of enteral feeds in infants fed with preterm formula compared with term formula and investigated the effects of different formulas on intestinal motility[147]. Fifty-two preterm infants who were receiving parenteral nutrition (PN) were randomly assigned to small volume (24 ml/kg/day) supplemental enteral feeds for 10 days with either term or preterm formula. Feeds were given in 4 hourly cycles, with continuous feeding for 2 hours and rest for the next 2 hours. Motor activity was measured using manometry on the day of starting enteral feeding (pre-test) and again 10 days after repeated enteral feeding (post-test). A subgroup of infants was fed both types of formula during the pre-test. Gut responses were similar between the groups in the fasting state. All infants demonstrated a change in motor activity at the onset of enteral feeding, but the response differed with the type of formula. Infants fed term formula showed an increase in contractile activity when feeding commenced; in contrast, those fed preterm formula showed a decrease in motor activity, which was greatest at 60-90 minutes of feeding. Similarly, in infants where both types of milk were given sequentially, motor activity was increased initially in response to term formula, but this was followed by a decrease with preterm milk. By the time of the post-test responses were similar in both groups. Of the 9 infants who experienced feed intolerance during the study period, 7 were in the preterm formula group. Feed intolerant babies went on to establish full enteral feeding later (22 v 11 days). Neither of these results reached statistical significance due to the small number of babies. The authors speculated that these differences related to the different composition of the feeds and principally the higher fat and carbohydrate content in preterm formula. Feeds containing high levels of carbohydrate and fat content have also been shown to inhibit gut motility and gastric emptying in adults[148].

It appears that both beneficial and non-beneficial effects exist with the use of preterm formula in infants where breast milk is not available. In practice, the choice of which type of

formula to use probably rests with the clinician, with decision-making likely to be based on his or her interpretation of this data in the absence of a large body of research evidence. Potential long-term benefits of improved developmental outcome are indeed attractive, but may appear less convincing if weighed against the risk of longer duration of central venous parenteral feeding and potential for life-threatening infection that may be associated with this.

(d) Hydrolysed protein formula

Grulee and Sanford first highlighted a link between formula feeding and the development of infantile eczema in 1936[149]. Since this time, efforts have been directed towards reducing the risk of allergy in babies by modification of feeding. The use of protein hydrosylate formulas for infant feeding was first introduced with the aim of preventing and treating cow's milk allergy in term infants. A recent systematic review of the literature identified 2 studies comparing early feeding with hydrolysed formula and breast-feeding[150 151], and 16 comparing prolonged feeding with either extensively or partially hydrolysed formula and cow's milk formula[152-166]. Studies comparing human milk and hydrolysed formula found no difference in the incidence of allergy, but these were only short-term trials. Meta-analysis of trials comparing hydrolysed protein formula with cow's milk formula showed a significant reduction in early allergy, but this failed to reach significance when the incidence of allergy at 2 years was considered. Studies included in the analysis were small and heterogeneous with respect to definitions of allergy and atopy was not always confirmed with allergy testing. Most studies[152-154 156-159 162 163 165 166] recruited infants at high risk for allergy based on family history. Two recruited healthy term babies[150 164] and only three studies enrolled preterm and/or low birth weight infants[155 160 161]. No adverse effects were found in term infants, but preterm infants were at increased risk of poor weight gain when fed hydrolysed formula. The authors concluded that there was insufficient evidence to recommend hydrolysed formula feeding above exclusive breast-feeding for the prevention of allergy or food intolerance, but that limited evidence exists that supplementation with hydrolysed formula in preference to cow's milk formula may be of benefit in infants at high risk of allergy who cannot be exclusively breast fed.

Hydrolysed formula use has also been suggested to improve early tolerance of enteral feeds in preterm infants where breast milk is unavailable. In a study of 36 infants, Riezzo *et al* randomised infants who were taking full feed volumes by bottle to receive either standard preterm formula or hydrolysed formula and measured gastric electrical activity and gastric

emptying time[167]. There was no significant difference between the groups for either parameter. Although infants receiving hydrolysed formula had less episodes of vomiting, this difference was not significant. Mihatsch *et al* studied 15 preterm infants taking full enteral feeds including up to 20% of their feed volume as maternal breast milk in a randomised crossover study[168]. The first formula was fed for 5 days before changing to the second for a further 5 days. Carmine red was used to stain the milk on days 4-9 of the study and the time from feeding the dye until its appearance in the nappy was recorded as the transit time. Transit time was shorter in infants fed hydrolysed protein formula (9.8 hours v 19 hours). There were no differences in the number of episodes of vomiting or the gastric residual volumes representative of feed intolerance.

3.4.3.3 Minimal enteral nutrition

Surges in the gut hormones, motilin, gastrin and enteroglucagon have been demonstrated in response to enteral feeding during the early postnatal period[169]. These physiological responses occur in both term and preterm infants and are thought to be an important element of adaptation after birth, stimulating trophic changes in the structure and function of the neonatal gut in preparation for extrauterine nutrition. The fact that these responses were not seen in infants that had not received milk feeds led to investigation of the hypothesis that enteral feeding is essential for normal gut maturation in the newborn. Animal studies have shown that hypotrophy of the gut occurs in neonatal rats who have received only PN for even a small number of days[170]. Lucas first investigated the amount of enteral feed necessary to induce postnatal gut hormone responses[171]. The results of his study suggested that volumes of breast milk equating to 1ml/hour for 24 hours was sufficient to induce significant hormonal surges and that by the time a total of 96ml had been given, hormonal responses were maximal. The authors concluded that "the first few millilitres of milk to enter the gut may constitute a potent stimulus to gut development which could then precede the attainment of full enteral feeding", whilst recognising that such small feed volumes were not adequate from a nutritional point of view. Berseth and colleagues demonstrated that gut motility differed between term and preterm infants, but that infants born as early as 25 weeks of gestation showed changes in the motility of the small intestine in response to infusion of milk feed[172]. They also showed that infants given early milk feeds showed enhanced maturation of gut motor responses and increased production of gastrointestinal peptides compared with those in whom feeding was delayed. Early milk feeding was also associated with improved feed tolerance and earlier achievement of full enteral feeding[173 174].

The practice of early administration of small volumes of milk alongside PN with the aim of promoting normal intestinal structural and functional development has been variously referred to as minimal enteral feeding, minimal enteral nutrition (MEN), gut priming, trophic feeding and hypocaloric enteral feeding and these terms have been used interchangeably in studies. Several randomised trials have been conducted to investigate the effects of minimal enteral nutrition, compared with fasting, on important feeding-related outcomes[175-183]. These have been small, single-centre studies and have used slightly different definitions of MEN. Initiation of MEN started between day 1 and day 4 of life; volumes given ranged from 10ml/kg/day to 25ml/kg/hour; frequency of feeding ranged from hourly to 4 hourly and the duration of MEN continued for between 7 and 14 days. One study continued MEN until ventilation was discontinued[176-178] and another until umbilical artery catheters were removed[184]. In most cases, MEN was given as EBM or formula, but two studies excluded breast fed infants[175 179]. In all trials, controls received no milk and all infants received PN during the period of study. A Cochrane review reported a meta-analysis of these trials[185]. This did not show any significant difference between infants receiving MEN and those that did not in the time to achieve full enteral feeding or NEC. No statistically significant differences were found in mortality, short-term measures of growth or hospital stay between the two groups.

Two recent studies have addressed other specific outcomes with respect to MEN. Weiler *et al* assessed bone mass at term corrected gestational age in infants born between 24 and 32 weeks of gestation who were fed MEN of 12ml/kg/day[186]. In this randomised trial, MEN was commenced either before or after 72 hours of life and typically between 2 and 6 days. The authors showed a significant increase in bone mineral content in infants receiving MEN compared with those that only received PN. However, this small study included only 27 infants and there were a number of deviations from the intended protocol, so it is possible that the positive result may represent a type 1 statistical error. Henderson *et al* used a case-control study design to examine the relationship between enteral feeding regimens and NEC[187]. Cases were infants born at less than 37 weeks of gestation with NEC, diagnosed according to modified Bell's criteria. Controls were matched for gestational age. Although the mean time of commencing feeds (cases 2.9 days v controls 2.8 days) did not differ between the two groups, cases diagnosed with stage II/III NEC received shorter duration of MEN (<1ml/kg/hour) than controls (3.3 days v 6.2 days).

One randomised trial is often cited in support of the protective effects of prolonged small feeding volumes against NEC[188]. Berseth *et al* randomised 141 preterm infants to receive either minimal feeds of 20ml/kg/day for 10 days or increasing feeds, advancing by 20ml/kg/day from the time at which enteral feeds were introduced, which was determined by the attending neonatologist. A sample size calculation a priori had determined that recruitment of 250 infants would be required to detect a decrease in incidence of NEC from 12% to 4% with a power of 0.8 at the 5% significance level. Unfortunately, the study was discontinued early because of a significantly higher rate of NEC in the group assigned to advancing feeds (10% v 1.4% ($P<0.03$)), determined by a one-tailed Fisher's exact test. The combined outcome of NEC and death showed no statistically significant difference between the groups. Although the authors did not specifically state the age of starting enteral feeds, the data published suggested that the mean day on which enteral feeds were introduced was around the tenth day of life. This implies that all babies experienced a period of starvation, in contrast to most studies of MEN, in which enteral feeds are introduced during the first week of life. The authors' conclusion that prolonged use of small enteral feedings reduces the risk of NEC has been questioned and it is clear that caution is necessary in interpretation of these results[189].

None of the studies of MEN has assessed long-term outcomes and none attempted to determine either the optimal time for starting minimal enteral nutrition or the duration for which minimal enteral feeding should be given.

In the absence of conclusive evidence for the practice of MEN, researchers have sought to determine current practice among clinicians. A survey of Australian neonatologists in 2001 yielded a response rate of 70% (56/80)[190]. Of the respondents, 80% prescribed trophic feeding for infants born at 27 weeks of gestation and less. Reported volumes given were 1-30ml/day or 10-30ml/kg/day. Approximately half of the clinicians would continue MEN for 2-3 days, whereas the remaining half would continue for 5-15 days. Results of a North American survey, conducted in 2006 were recently reported[191]. This survey was distributed to neonatologists, neonatal nurse practitioners and dieticians, with a response rate of 23% (176/775). The majority of respondents indicated that they prescribed MEN and continued this for longer in the smallest babies. The duration of MEN reported varied between 0 and 10 days. This reported variation suggests that lack of evidence has led to a wide range of clinical practice with respect to the use of MEN. In spite of positive results in physiological studies and the now widely held view that MEN may be beneficial for high risk infants,

objective data remains limited, uncertainty exists about how best to achieve positive effects and further studies are warranted to guide clinical practice.

3.4.3.4 Timing of introduction of enteral feeds

The timing of initiation of enteral feeding in preterm neonates is dependent on many factors related to inherent features of individual babies such as gestational age at birth, birth weight and severity of illness but also to preferences of clinicians. However, the success in establishing early feeding is also related to the structure and function of the preterm gut, which differs from that of more mature infants and adults[192].

Aspects of gut maturation have been studied in preterm infants, with much of the research examining development of gut motility and the intestinal response to feeding. Berseth characterised gut motility in 31 infants who had never been fed, using continuous manometry[192]. The gestational age of the infants ranged from 25-42 weeks and studies were carried out 12 hours before the introduction of enteral feeds. Term born infants showed similar patterns of gut activity to those demonstrated in adults, consisting of three phases: (i) periods of quiescence, (ii) irregular activity and (iii) periods of regular phasic propagating activity, also known as migrating motor complexes (MMCs). In contrast, MMCs were not present in the majority (19/23) of preterm infants and when they occurred were of lesser amplitude than in term infants. A further study using similar methods in 36 infants examined the response to initiation of continuous, slow formula feeding[172]. Results showed increases in motility from the fasting state in both term and preterm infants that were not significantly different, suggesting that infants as immature as 25 weeks of gestation are able to respond to enteral feeds. The effect of timing of introduction of enteral feeds in preterm infants was studied, using manometry and measurement of intestinal peptides, in a group of 27 ventilated infants of whom 14 received early (postnatal day 3-5) formula feeds and 13 received late (day10-14) feeds[173]. These infants were more mature, with gestational ages of 32 ± 1 weeks. An initial study was performed before enteral feeds up to day 5 of life, a second at 10 days and a final study after a further 10-14 days. Feeds were commenced at 1ml/hour and advanced daily by 1-2ml/hour until a daily volume of 120ml/kg was achieved. Results showed significant differences in intestinal motor activity, but not in intestinal peptide activity between the groups at the time of the first study. At the time of study 2, early fed infants showed better organisation of gut motor activity and increased gut hormone and peptide activity compared with those fed late. By the third study period, results were the same in both groups, with 75% of babies showing distally migrating MMCs. Early feeding

led to earlier establishment of full enteral feeds (day 17 versus day 31 (P<0.01)) earlier oral feeding (day 35 versus day 47 (P<0.05)) and shorter hospital stay (38 v 55 days (p<0.05)). Late fed babies also showed greater feed intolerance than the infants fed early. This study suggests that earlier introduction of milk feeds is beneficial for promoting maturation of the gut and moreover, that delaying feeding may hinder gut development and adversely affect clinical outcomes such as growth. Later studies showed similar advantages in introducing milk, rather than water feeds in preterm infants, indicating that nutritional feeding is important in the process of gut maturation after birth[174 193].

Other studies and trials investigating the effect of early and late introduction of feeds on clinical outcomes in less mature babies have been diverse with respect to timing and volumes of feeds administered. In all studies, infants were given PN until attaining adequate enteral feed volumes. Slagle and Gross randomly assigned 46 preterm neonates of $\leq$ 32 weeks and birth weight $\leq$ 1500g either to receive milk feeds of 12ml/kg/day from day 7 or to starve for a further 10 days before advancing feeds on day 18 of life[194]. The type of milk given in this study was not standardised. Early fed infants showed better tolerance of feeds and had shorter duration of PN.

A number of researchers have sought to determine whether timing of initiation of feeds plays a role in the development of NEC. All studies have been small and many observational. LaGamma *et al* used a scoring system to identify "sick" infants at risk of NEC[195]. These infants were assigned, at the discretion of the attending clinician, to receive no milk feeds for two weeks (n=20) postnatally or to receive incremental dilute formula or breast milk feeds during this time although it is unclear exactly when enteral feeds were started in the early feeding group. In this study, infants receiving no enteral feeds had a higher rate of NEC (60%) than those given milk in addition to PN (22%). The authors came to the conclusion that "early, dilute, incremental oral feedings that are gradually advanced may serve to protect the human gut". However, given the small numbers included in the study and the retrospective design, it would not have been possible to detect differences in the occurrence of NEC with certainty. A further small study by the same research group attempted to define an optimal time for introducing feeds[196], assigning high risk babies to starting enteral feeds on day 1 (n=18) or day 7 (n=20) of life, progressing from sterile water, to dextrose 2.5%, to dilute milk feeds and finally to full strength feeds over seven days. Feeds were advanced after seven days. The incidence of NEC in this high-risk group was similar regardless of feeding (5/17 early v 6/17 late fed infants) but, as in the previous study, there was

insufficient power to detect a true difference. Dunn *et al* randomised 39 ventilated infants of <1500g birth weight with UACs to commence enteral feeds of 15-20ml/kg/day of dilute formula at 48 hours or 10 days of life[175]. The attending clinician decided rates of feed advancement after 10 days. Infants fed early in this study showed earlier attainment of full enteral feeds and required less days of phototherapy for jaundice. This small study was also unable to detect a statistically significant difference in rates of NEC between the early and late fed groups (5% and 16% respectively). A case control study by McKeown *et al* examined records of 59 pairs of infants matched for race, date of birth and birth weight[197]. Their analysis revealed that the number of infants developing NEC who had been fed prior to diagnosis was significantly greater than the number of controls fed during the same period. In the NEC group, enteral feeds had been commenced significantly earlier than in controls (mean 5.1 (SD2.2) v 7.7 (5.1) days ($P<0.01$)). This remained significant after controlling for birth weight and risk score.

Only two randomised controlled trials, one published only in abstract format, have addressed this issue. Davey *et al* randomised 62 infants with low UACs to early (median 2 days) or late (median 5 days) introduction of feeds[198]. Feeds were of whey, breast milk or diluted formula using identical feed volumes and rates of advancement. There were no significant differences in morbidity between the groups, but infants receiving early feeds were evaluated less for sepsis and received less days of PN. The authors concluded that there was no disadvantage to early feeding of preterm infants with low UACs. Khayata randomised only 12 infants to early (within 4 days of birth) or late (day 10) feeding with standard formula milk[199]. This study reported no difference in weight gain between the groups, but did not include NEC as an outcome.

Of note is the fact that feeding protocols in the studies discussed have used water, glucose solution or formula feeds. Only a small number of babies in one small study received maternal breast milk. Later studies have included infants fed EBM. Sisk *et al* recruited a cohort of very low birth weight infants to examine the effects of early maternal expressed milk (MEBM) feeds[200]. Formula milk was given only if the mother chose to formula feed or had insufficient breast milk and enteral feeds were started when the infant was deemed stable by the attending clinician. In this study 72% of infants started feeds within the first 3 days of life and 97% within one week. Infants who received $\geq$ 50% of their enteral intake as human milk (n=156) within the first two weeks of life were significantly less likely to develop NEC than those whose breast milk intake was <50% of the total (5/156 v 5/46). The authors

concluded that the type of milk, rather than timing of introduction or volume given may be more relevant when considering the effects of feeding on the incidence of NEC. In a large cohort study of Norwegian infants of <1000g, Ronnestad examined the effects of very early feeding with human milk[201]. Feeding was started within a few hours after delivery at volumes of 1-2ml every 2 or 3 hours, increasing by 0.5-1ml every 6-8 hours. Feeds were started on day 1 in 61%, by day 2 in 91% and by day 3 in 96% of enrolled infants. Clinical signs suggestive of NEC were noted in 4%, with only 2.2% having radiological evidence of pneumatosis intestinalis. Rates of late onset sepsis were reduced in infants who achieved full feeds earlier, but no effect on sepsis was seen related to the time of commencing feeds. However, this may be due to the fact that feeds were started early in most babies and 80% had achieved full enteral feeds by 14 days of life. This study suggests that it may be possible to feed infants with EBM considerably earlier than attempted in most studies without complications.

Few studies have sought to determine the optimum time for introducing enteral feeds in preterm infants in the current era of neonatal intensive care and none have been randomised. Studies that have been conducted vary considerably with respect to type and timing of milk feeds and whether static minimal feed volumes or progressively increasing volumes are given. None had large enough sample sizes to detect a difference in the incidence of NEC reliably. Variation appeared to stem from differing local practice between centres and countries, differing interpretation of the published literature and likely differing experiences and preferences of individual clinicians. Systematic reviews have suggested that further work is necessary to inform clinical practice with respect to the introduction of either minimal or progressive enteral feeds[185 202]. Although many individual NNUs may have written local guidelines, given the paucity of robust evidence, no clear national or international guidelines have been produced to assist clinicians in their daily practice. However, recent papers[203 204] have suggested that minimal enteral feeds of 5-20ml/kg/day, using human milk where possible, should be started within the first one or two days of life.

3.4.3.5 Rate of advancement of enteral feeds

Whilst the introduction of small volume feeds is thought to enhance development of motor activity in the preterm gut, it is clear that, at some point, these volumes must be increased to establish full enteral nutrition adequate for growth. The aim of neonatal nutritional care in high-risk infants is to achieve this as soon, but as safely as possible, without increasing the rate of serious complications. It has been suggested that fear of NEC may interfere with

consideration of other important outcomes, which may be both positive, such as growth, and negative. Since the provision of early nutrition demands the use of parenteral feeding, usually administered via central venous catheters, the risks of prolonging PN include catheter-related complications such as septicaemia and less commonly, cardiac tamponade. Complications of PN administration itself include liver impairment, cholestatic jaundice, hyperlipidaemia, and electrolyte disturbances. Rapid advancement of enteral feeds, therefore carries benefits, but it has also been associated with an increased risk of NEC.

Book *et al* first compared two different rates of feeding in a retrospective study prompted by an observed increase in NEC from 0.3% to 5.1%[205]. This showed that infants developing NEC achieved full enteral feeds more rapidly (day 7) than those who did not (day 14) and that the average daily feed volumes were twice as large in these infants. They then randomised 29 infants to slowly increasing feeds (10ml/kg/24 hours) or rapidly increasing feeds (20ml/kg/24 hours). Feeds were started at a mean age of 2.9 and 2.3 days respectively. This prospective study was not able to detect a difference in rates of NEC between the groups due to its very small sample size. The difference between slow and fast regimens was small and in terms of today's practice, both may be regarded as slow or even minimal feeding. Goldman further highlighted a possible link between feed volumes and NEC in 1980[206]. He observed a sharp increase in NEC in infants <2500g with a change in feeding policy characterised by larger increases in feed volumes. However, this was a diverse group of infants of varying birth weight, severity of illness and seven different types of formula feed were used. In addition, increases in volumes were variable, with some as high as 60ml/kg/day, which represents much larger increases than seen in most other studies, or in clinical practice today. The multicentre study by Uauy *et al* showed that, in a cohort of 2681 infants at risk of NEC, the most significant factor predicting the prevalence of NEC was differences between centres[7]. They observed that infants who regained their birth weight more quickly were at increased risk of Stage II and III NEC. Although they were cautious in their interpretation of this observational study, they suggested that, amongst other factors, aggressive fluid and feeding regimens might contribute to the prevalence of NEC in VLBW infants. McKeown *et al*, in a case control study found that the 59 cases were fed earlier, were given full strength feeds earlier and were fed more rapidly than controls, with sicker infants being more vulnerable[197]. They estimated infants fed with increasing volumes of more than 30ml/kg/day to have a 28-fold risk of developing NEC, but the 95% confidence interval for this result is wide (OR 28.0 (CI 3.81-205.8)).

There are few randomised controlled trials addressing the question of the rate at which enteral feeds should be advanced. A major difficulty with randomised feeding trials is the inability to use blinding, potentially introducing bias. This can be minimised by concealment of the randomisation process, the use of strict study protocols and independent observers for outcomes, such as radiological evidence of NEC and by the use of intention to treat analysis.

Rayyis *et al* randomised 185 formula-fed infants with birth weight <1500g and gestational age at birth of ≤34 weeks to slow feeding (20ml/kg/day increasing by 15ml/kg/day) or fast feeding (35ml/kg/day increasing by 35ml/kg/day)[207]. MEN was not used in this study and feeds were started on day 4 or 5 of life. Breast fed infants were excluded, as were those requiring inotropic support, those with congenital heart disease, polycythaemia or requirement for exchange transfusion. The trial used a defined protocol for the temporary discontinuation of feeds based on gastric residual volumes and abdominal examination. Independent radiologists performed reviews of all x-rays to diagnose NEC. The sample size was based on 16% of infants expected to develop of NEC with fast feeding, and the detection of a fall to 5% in the slow feeding group. No statistically significant difference was seen in the incidence of Bell stage II or III NEC between the randomised groups (13% for slow feeding v 9% for rapid feeding). Of note is the fact that neither group reached the anticipated proportion of 16%, which had been observed prior to the trial and was used to determine the power of the trial. Babies allocated to rapid feed advancement achieved full enteral feeds by 11 days compared with 15 days in the slow group (P<0.001) although the length of hospital stay was similar in the groups. Caple *et al* randomised 155 infants between 1000g and 2000g birth weight and ≤35 weeks of gestation at birth to either slow (increments of 20ml/kg/day) or fast (increments of 30ml/kg/day) feeding[208]. Breast milk was used where possible and this was similar (32-34%) in both groups. Criteria for stopping feeds were defined *a priori*. The primary outcome for this study was the time to full enteral feeds of 150ml/kg/day and infants assigned to the faster feeding regimen achieved this 3 days earlier than the slow group (P<0.01). They also had significantly fewer days of intravenous feeding (P<0.01) and a shorter length of stay, although the latter difference was not statistically significant. Three infants in the fast feeding group developed NEC compared with two in the slow group, with an overall rate of 3.2%. The day of starting feeds was determined by the attending clinicians and is not stated for either group. The study is also limited by the researchers' decision to exclude babies weighing <1000g, their justification being that there is often a delay in starting feeds in this group. Unfortunately, this group is the most vulnerable and high-risk group for NEC and therefore the group for whom data is much

needed. A meta-analysis of these three randomised trials was performed in 1999 and showed a reduction in days to full feeds and days to regain birth weight[209]. However, the small number of infants included and low overall rates of NEC with wide confidence intervals meant that the effects of different feeding regimens on NEC could not be determined with certainty. Much larger multicentre trials, preferably including infants at highest risk, would be required to assess this important outcome. Authors of a more recent Cochrane review in 2008 chose to analyse the role of slow advancement of feed volumes to prevent NEC in very low birth weight infants[210]. In this review, the study by Book[205] was excluded because feeds in both groups were advanced slowly. Perhaps because of the challenges associated with designing large randomised controlled trials of feeding practice, it is interesting to note that only one additional small trial met the criteria for inclusion in this review. Salhotra and Ramji included infants <1250g who were given 2-3 days of minimal enteral nutrition of 5ml/kg/day before increasing to 15ml/kg/day followed by increments of either 15ml/kg/day (n=26) or 30ml/kg/day (n=27)[211]. In this study, full enteral feeds were defined as 180ml/kg/day and preset criteria for feed discontinuation were used. As with previous studies, some of the infants at highest risk were excluded because of the need for inotropic drugs or oxygen therapy. The mean gestational age and birth weight of included infants were 33 weeks and 1050g respectively. Results showed that fast fed babies achieved full feeds 5 days earlier ($P<0.001$) and had better weight gain but the study was not large enough to detect any difference in NEC, which occurred in only two babies, both assigned to rapid feed advancement. The Cochrane meta-analysis was unable to show evidence of benefit with slow advancement of feeds, due to the same reasons identified in the earlier review.

Substantial uncertainty remains regarding the optimum rate at which feeds should be advanced in high-risk preterm infants. Studies have been small, methods and outcomes different, and results inconclusive. Rapid advancement has consistently, but not surprisingly, resulted in the earlier attainment of nutritional feed volumes and therefore reduced exposure to the risks of PN. Short-term measures of growth have also been improved in this group. Although observational data suggest that rapid feeding may be associated with an increased risk of NEC, randomised trials to date have not confirmed this finding. However, in reality, no trial has been performed that would have adequate power to demonstrate this difference. No trial of the rate of feeding has examined longer-term outcomes, such as neurodevelopmental outcome or later growth parameters. Most studies have centred on formula-fed infants and there are few data indicating whether suggested risks of rapid feed

advancement are similar in infants who are either exclusively or primarily fed EBM. Indeed, it seems plausible that the optimum feeding regimens may be different depending on the type of milk given, but this has not been adequately explored. Few extremely low birth weight or severely ill neonates have been included in studies, and these are also groups for whom feeding needs may be different. In spite of the challenges associated with large trials that investigate uncommon outcomes, it is unlikely that these questions will be answered without such research.

3.4.3.6 Standardised feeding regimens

The large variation in incidence of NEC has, over many years, led researchers to question whether difference in "packages" of clinical care given to preterm neonates in neonatal centres is important in causing or preventing the disease[7]. In many NNUs, local guidelines have been introduced, based on available evidence, in an attempt to standardise management in the hope of reducing NEC and improving outcomes for babies. A report of variations in incidence of NEC in Canadian NNUs included 18,234 infants admitted to 17 neonatal intensive care units between 1996 and 1997 showed no significant difference in risk-adjusted incidence between units [64]. However, one unit included in this study reported no NEC among 910 admissions during this period. It is possible that this finding over a two-year period was as a result of chance, particularly since the incidence of NEC is known to fluctuate with time. However, the same centre also reported that they had no cases in the five-year period preceding the study. This led the authors to conclude that "it may be possible to reduce the incidence of NEC through selected practice changes" although the study did not specifically collect data on feeding practices within the NNUs. Wiedmeier et al documented the incidence of NEC in three units over a four-year period, during which one of the three centres experienced a rate of 14.5%, compared with 2.3% in each of the other two centres[212]. This study examined demographic data, maternal and infant characteristics and a number of areas of clinical practice, including feeding of infants to try to explain this difference. Their analysis revealed that feeding practice in the centre with the highest incidence was clinician-dependent, whereas the other centres used detailed written feeding guidelines. They also showed an increased incidence in black infants, although the number of such infants was small in all centres. Although ethnicity and the number of outborn infants varied between centres, they were not thought to account for the differences in NEC. Feeding schedules in the two hospitals with low incidence were most notably similar in their greater use of human milk and this may reflect the protective role of breast milk as shown in previous studies.

However, other authors have postulated that standardised feeding guidelines may play an important role in the prevention of NEC in preterm infants.

In 1978 Brown and Sweet reported their experiences following the introduction of a new "cautious" feeding regimen for preterm infants[213]. They described in detail their slowly progressive feeding schedule, which they believed had "virtually eliminated" NEC from the unit over a four-year period compared with their previous feed management. Spritzer later reported similar findings in a sequential study before and after the introduction of a more cautious feeding regimen for infants <2000g[214]. Their management of infants at high risk for NEC changed from a first feed of 20-40ml/kg/day of full strength formula, given at the discretion of the neonatologist, increasing by 20-40ml/kg/day. The later regimen involved withholding feeds for one week before giving diluted formula at 20ml/kg/day, increasing by 20ml/kg/day. With this change, they saw a dramatic and prolonged reduction in NEC from around 13% to zero over a seven-year period. Kamitsuka *et al* retrospectively reviewed records of infants over a six-year period during which a standardised feeding protocol was introduced[215]. Prior to this, feeding practices varied for babies of ≥1250g although smaller infants were already fed according to a defined protocol. When developing the protocol, they considered the time of starting feeds, rate of advancement and concentration of feeds and devised different protocols for three groups of infants according to birth weight: (A) 1250-1500, (B) 1501-2000g and (C) 2001-2500g. The groups were starved for at least 72, 48 or 24 hours respectively and longer if clinically indicated. First feeds were of either breast milk or diluted formula, changing on day 4 of feeds to full strength. Daily feed volumes were increased by no more than 20ml/kg/day and full feeds were established for the groups in 10, 9 or 8 days. During the non-standardised period, 4.8% (23/477) of infants developed definite NEC, compared with 1.1% (5/467) after introducing the regimen (P=0.0006). The difference in babies fed with breast milk was less marked, with the reduction being 60%. However, a significantly greater proportion of babies received breast milk in the second part of the study period, which may also have influenced the rates of NEC. Patole *et al* also report virtual elimination of NEC over a period of 5 years with standardised feeding introduced because of participation in controlled trials compared with a historical cohort of babies[216]. Only one case of NEC was seen after introducing standardised feeding, compared with six deaths attributed to the disease in the previous five-year period. The components of the new feeding regimen were not substantially different from the clinical practices in the unit beforehand, except for the management of feeds in infants with haemodynamically significant patent ductus arteriosus (PDA), but they were unable to comment on whether this factor might have

influenced NEC rates independently. Premji *et al* used a before-and-after matched cohort study to assess the benefits of a clinical practice guideline for feeding in infants <1500g[217]. Matching was performed for birth weight and gestational age in 100 babies in line with an a priori sample size calculation based on pilot data. In contrast to other studies, the results showed no statistically significant differences between the groups for time to full enteral feeds, day of commencing feeding, feed intolerance, days of receiving PN or the incidence of NEC.

The largest study to address the value of standardised guidelines is reported by Kuzma-O'Reilly *et al* on behalf of the Vermont Oxford "Got Milk" focus group[218]. This group developed guidelines for potentially better practice for feeding based on eight evidence-based criteria for the initiation and advancement of enteral and parenteral nutrition and monitoring of feed-related outcomes. These were instituted in three participating centres, all of which were involved in the guideline development. Membership of the VON permitted benchmarking of these unit outcomes against other member centres. Following implementation of the guidelines, the group showed reduction in the time to starting feeds and achieving full feeds, increased use of breast milk as the first feed and earlier initiation of parenteral feeding. There was a reduction in NEC from 16% to the VON mean of 6%.

Patole and de Klerk performed a systematic review of some of these observational studies[219]. Although there was significant heterogeneity between the included studies (P<0.001), they performed a meta-analysis. Inclusion of all studies[213-219] revealed that the risk of NEC was reduced by 87% (Pooled risk ratio 0.13 (95% CI 0.03-0.5) following introduction of a standardised regimen. A second meta-analysis of studies that included VLBW infants[215-218] [220] suggested a smaller reduction of 47%, with the study by Patole *et al*[216] [220] showing the largest effect. Exclusion of this study from the analysis reduced heterogeneity between the studies to a level that was not significant and this analysis suggested an overall reduction in risk of NEC of 29% associated with the introduction of any standardised feeding regimen. The authors conclude that standardised feeding regimens may represent "the single most important tool to prevent/minimise NEC".

It is difficult to interpret data from such studies reliably. The included studies were conducted over a period of many years, during which neonatal care has progressed, in terms of both the population requiring intensive care and the treatments available to clinicians. Many of these factors may influence changing outcomes. The use of before-and-after

analysis is also subject to confounding within individual studies due to other local changes in clinical practice, patient population and staff over time. Caution should therefore be exercised in attributing reduction in adverse outcomes entirely to the introduction of a new policy. Since differences in the policies existed between the studies, this implies that, rather than content of the policy being the most important factor, the mere existence of a unit guideline influenced outcome. This is difficult to explain. Unfortunately, none of these studies showed evidence of monitoring of strict compliance with the policy and it cannot be assumed that adherence was universal.

3.4.3.7 Fortification of breast milk

Whilst there are many clear benefits to feeding with breast milk, human breast milk does not provide sufficient protein, sodium, calcium or phosphate to fully meet the nutritional needs of the preterm infant[221]. The nutritional content of milk from mothers delivering preterm is similar to that of term milk by 3 or 4 weeks after birth, a time of very high nutritional demand for the baby, considerably in excess of that in a healthy term baby[222]. Inadequate nutrition at this time can have long-term effects on growth and development. Low mineral intake in infants fed solely on breast milk places them at risk of decreased serum phosphate levels, increased calcium levels and increased alkaline phosphatase (ALP) activity compared with infants fed preterm formula, which is specifically designed to meet these needs[223]. Osteopenia of prematurity is common in preterm infants due to delayed feeding and lack of active movement and this is further exacerbated by inadequate intake of essential minerals. Protein content is variable in breast milk and may also be inadequate. In practice, one potential response to this situation is to change from breast milk to formula feeding, but this approach deprives high-risk infants of the beneficial effects of breast milk and is unacceptable to many mothers who wish to establish breast-feeding at later stage. To overcome this, methods of fortification based on cow's milk have been developed for addition to human milk, the most commonly used being powders containing multiple nutrient components including protein, fat, minerals, electrolytes, vitamins and trace elements[224].

Growth in infants fed fortified human milk does not reach the rates seen in formula fed infants. Schanler *et al* compared infants receiving either fortified breast milk or preterm formula[225]. Infants receiving fortified breast milk showed better tolerance of feeds and attained full enteral feeds earlier, although both groups attained full oral feeding at a similar time. This group also experienced significantly lower rates of NEC than the formula group

(1.6% v 13% (P≤0.01)). However, rates of growth in these babies were significantly lower than in the formula fed group. The authors concluded that the benefits of feeding with human milk fortifier (HMF) outweighed the disadvantage in growth.

Several studies made additional comparisons between preterm formula, fortified breast milk and unfortified breast milk. These studies were diverse with respect to entry criteria, volumes of milk given, components and amounts of the fortifier used, and outcome measures. Most evaluated growth in some way and some included measurements of bone mineral content. Human milk in all studies was either mother's own milk or donor breast milk, depending on availability. Carey analysed data from 18 infants of birth weight <1500g, randomised to one of three groups: human milk with or without fortification or preterm formula[226]. Fortification included protein, calcium and phosphorus. The milk protein content differed between the groups but energy content was similar. The study protocol continued for around one month. This small study showed increased weight gain (g/kg/day) in the groups fed fortified human milk or formula compared with infants receiving only unfortified breast milk. Both human milk groups showed low phosphate levels and high ALP levels compared with formula fed infants. Venkataraman studied 24 infants <1500g in a similar study and also showed raised ALP levels with feeding of non-fortified human milk, but not in the other groups[227]. Outcomes were evaluated after 2 weeks. This study also measured bone mineral content by direct photon absorptiometry and found this to be lowest in the non-fortified human milk group and highest in the formula fed group. Weight gain was not measured. In a study by Modanlou *et al*, 30 very low birth weight infants were assigned to similar groups and were evaluated at the time of discharge or when the weight had reached 1800g[228]. Their HMF contained additional protein, calories and minerals. This study also showed poorer weight gain (g/day) and slower increase in head circumference in infants fed unfortified human milk, but the authors were unable to show a difference in bone mineral content between the randomised groups. Nicholl and Gamsu used a HMF containing protein, carbohydrate, calcium, phosphorus, minerals and vitamins in a study randomising 52 infants[229]. Weight gain (g/kg/day) was highest in the formula fed infants and similar in both groups receiving human milk. Linear growth was measured using changes in lower leg length velocity and this was significantly greater in infants fed preterm formula or fortified human milk that those given human milk alone. Ronnholm studied 44 infants, randomised to receive unfortified human milk versus supplementation with either protein, fat or both[230]. This study showed increased gain in weight and length in the protein-supplemented groups and a decrease in protein levels in the group fed unfortified human milk, suggesting that

protein, rather than calorie content, is the most important factor influencing weight gain. Kashyap analysed data from 42 infants between 900 and 1750g birth weight, given mother's own milk either with or without supplementation containing protein, calcium, phosphorus and sodium[231]. A third group comprised infants who received supplemented donor breast milk. The results showed increased weight gain in the supplemented human milk groups compared with the unsupplemented group, but ALP levels did not differ. The degree of weight gain was proportional to the amount of protein fed, supporting the hypothesis that protein influences weight gain in these infants. Greer and McCormick included, in addition, a group of infants that were fed a standard term infant formula in a study of 38 infants[232]. They found that infants receiving either unfortified human milk or term formula took greater volumes of milk than the other groups. However, when evaluated after 6 weeks, these groups showed poorer weight gain (g/kg/day), poorer gain in length and head circumference and reduced bone mineral content compared with the infants who had been fed with fortified breast milk or preterm formula.

Others have examined the practice of using preterm formula as a supplement for human milk. Gross, in a study of 2 phases, compared unfortified human milk with supplementation using preterm formula after one week and supplementation using a powdered fortifier containing calcium and phosphorus after 2 weeks[233]. When all groups were compared, there was no difference between gain in weight, head circumference and length. However, secondary analysis showed significant increases in all parameters in the group receiving powdered fortifier compared with either of the other groups. After 5 weeks, there was no difference in the change in bone mineral content between the groups, although all were significantly less than those of healthy term babies. Interestingly, by the time of follow up at 44 weeks of gestation bone mineral content in these babies had increased to levels similar to term infants. This led the authors to conclude that fortification of human milk may not be necessary in healthy preterm infants, in view of the lack of evidence of long-term benefit. Zuckerman compared unsupplemented human milk with supplementation with preterm formula in 53 infants, only 20 of whom were followed up at 18 weeks after discharge[234]. They observed no rickets, found no differences in weight gain or length between the groups and concluded that supplementation of breast milk conferred no significant advantage over human milk feeding. One study compared only two groups with mean gestational age of 33 weeks, receiving either fortified or unfortified human milk[235]. They saw an increase in bone mineral content and faster return to birth weight in the fortified group. However, after

regaining birth weight, the rates of increase in birth weight (g/kg/day) were similar in the two groups and by 3 months of age, bone mineral content was similar.

A number of other studies chose to supplement the control group of unfortified milk fed infants with minerals. Faerk looked at 127 infants of <32 weeks' gestation in 3 randomised groups given human milk (mother's or donated) with added phosphate, human milk with protein, calcium and phosphate or preterm formula[236]. This study showed increased weight at term in the preterm formula group compared with the others, but no difference between the groups for head circumference, length or bone mineral content. Polberger compared supplementation of human milk with fat, protein or both and all included infants were also given supplements of vitamins, folate, calcium and phosphorus[237]. From 4 weeks, iron was also added. As shown in previous studies, growth was related only to the intake of protein. Large differences were seen in the amount of milk produced by mothers, which also varied in protein content. Wauben compared maternal breast milk supplemented with a multicomponent fortifier or phosphate and calcium alone with preterm formula[238]. Weight gain (g/kg/day) was similar in both groups fed human milk, but this was lower than those fed formula. There was no difference in bone mineral content between the groups.

Only one study addressed longer-term effects of human milk fortification[239]. Lucas randomised 275 infants of <1850g to receive fortification of maternal breast milk either with a multicomponent fortifier or phosphate, sodium, potassium and vitamins. Infants whose mothers were unable to produce sufficient breast milk were supplemented as necessary with preterm formula. There were no differences in the rates of growth between all groups, but those infants who received >50% of their intake as breast milk had increased weight gain (g/kg/day) than those receiving less breast milk. When followed up at 18 months, the fortified group attained higher scores on BSID, but this did not reach statistical significance.

The results of these studies are challenging to interpret because of the differences between them. There were very few infants of birth weight <1000g included in any of these studies. This is perhaps largely due to the fact that many were conducted when numbers of surviving babies of extremely low birth weight and gestational age were fewer. Most of the studies were also subject to large rates of attrition due to inadequate breast milk production, poor feed tolerance or illness in the babies. For many studies, the number of infants for whom data were analysed does not reflect the numbers that were initially recruited to the studies. This might introduce some bias in favour of infants whose mothers were able to produce

large quantities of breast milk and larger, healthier preterm neonates. The majority of these studies have included small numbers of infants. Kushel and Harding performed a Cochrane systematic review of thirteen randomised controlled trials[226 228 229 231-239] comparing human milk supplemented with multicomponent fortifier and unfortified human milk, including a total of over 600 infants[240]. Meta-analysis of these trials showed small but statistically significant increases in weight gain, head growth and linear growth in the infants fed fortified milk compared with unfortified milk. They did not show an effect on ALP levels. No short-term adverse effects were seen, although the small numbers and high attrition rates in most studies imply that cautious interpretation of this finding is required. No long-term advantage was found, although this was not addressed by most studies.

There has been concern clinically about feed tolerance in infants given fortified milk, although the definition of feed intolerance on which this may be based presents challenges. The Cochrane systematic review showed a trend towards increased feed intolerance, but this was not statistically significant[240]. Moody et al compared infants fed fortified human milk with infants fed unfortified human milk[241]. The mean gestational age and birth weight were 27 weeks and 1065g respectively and the infants received fortifier from 22 days of age. Although fortified infants had more episodes of gastric residual volumes >2ml/kg and more episodes of vomiting, this did not translate into a difference in the number of hours for which feeds were stopped, delay in attaining full feeds or hospital discharge. One of the proposed mechanisms for feed intolerance is delayed gastric emptying associated with the use of fortifier. Several studies have examined this, using paired studies of infants who were fed fortified and unfortified milk. McClure and Newell, in a study of 22 low birth weight infants found no influence on gastric empting[242]. Infants' median weight was 1495g and gestation 31.5 weeks; tests were carried out at 6-67 postnatal days. Gathwala used similar methodology in 25 babies with a mean gestational age of 34 weeks and birth weight of 1900g[243]. They also found no effect of fortification on gastric emptying. In contrast, Ewer and Yu found, in paired studies in 11 infants, that gastric emptying was slower in 10 of the 11 infants when fed fortified, as opposed to unfortified breast milk. These were less mature infants with median gestational age of 28 weeks and birth weight of 1090g. Given the effects of maturation on gut motility, it is possible that the conflicting results were due to the different gestational ages of infants studied. However, a recent study in 20 VLBW infants with mean gestational age of 29 weeks, found that although gastric emptying was reduced in infants when they were fed fortified milk, this did not reach statistical significance[244].

Some studies have included NEC as an outcome. In a prospective cohort study, Hallström studied risk factors for NEC in 140 infants[245]. Stage I-III NEC developed in 18.6% and severe (stage II-III) NEC in 8.6%. On logistic regression, the use of breast milk fortifier was significantly associated with all types of NEC (OR3.85, 95% CI 1.29-11.5 (P=0.016), but not with severe NEC. However, the infants developing severe NEC were significantly more immature and small than the rest of the NEC group. In their randomised trial, Lucas *et al* observed a non-significant trend (P=0.12) towards increased NEC in infants receiving fortified milk[239].

Increase in the osmolality of feeds has been suggested as a possible precipitating factor in NEC[246]. Jocson *et al* showed that the storage for 72 hours of fortified human milk increased the osmolality by approximately 4%. Others have since investigated the osmolality of fortified milk before and after storage for 24 hours. De Curtis showed that, with the exception of those containing only protein, addition of fortifiers rapidly increased the osmolality and a further increase was seen after storage[247]. Yigit also reported increased osmolality and found that it was highly variable between samples, but the time at which it was measured was not standardised [244]. Another study measured osmolality at 20 minutes and found a significant increase, but no additional change was seen at 6 hours[248]. Osmolality may vary with different types of formula and it is possible that this change may have different effects depending on the maturity of infants. No study has specifically examined this in a large group of infants.

Previously, HMFs have been derived from cow's milk. A recent development lies in the production of a new exclusively human milk-based fortifier, derived from screened human donor milk. Only one trial has so far studied this product[249]. 207 infants of birth weight 500-1250g were randomised to receive human milk-based fortifier when the enteral intake was either 40ml/kg/day or 100ml/kg/day or bovine milk-based fortifier when the enteral intake was 100ml/kg/day as a supplement to maternal or donor breast milk. Comparison between both human milk groups and the bovine fortifier revealed a lower incidence of NEC and surgical NEC in the human milk-based fortifier groups, both separately and combined. The reduction in NEC was 50% and for surgical NEC approached 90%. A statistically significant difference was found for the combined outcome of death and NEC (P=0.02). All cases requiring surgery were in the group fed bovine milk-based formula. The authors suggest that an exclusive diet of human milk may be important for protection. In one of the groups, fortification was started earlier and was tolerated well, which may have implications for

earlier and more appropriate weight gain. In addition, all infants in this study were less mature than in many other studies, so results may be more applicable to the current population of high-risk neonates. This may therefore represent an important advance in the enteral feeding of preterm babies.

3.4.3.8 Feeding preterm growth restricted infants

In view of the conflicting evidence with respect to NEC in growth-restricted infants, uncertainty exists about how enteral feeding should be introduced in these infants. This has led to the use of very heterogeneous feeding strategies among neonatologists. Research in this field reflects this uncertainty.

Several studies have looked at postnatal intestinal motility and tolerance of feeds in infants with abnormal Doppler studies. Robel-Tillig *et al* prospectively studied 124 infants with birth weight of less than 1500g[250]. This study found that 38/42 (88%) infants with prenatal haemodynamic disturbances had signs of intestinal motility problems including later tolerance of feeds and delayed passage of meconium, although none developed classical signs of NEC. These infants also had reduced blood flow velocity in the SMA supporting the hypothesis that poor gut perfusion may contribute to observed gut motility disturbances. Enteral feeding in these infants was started "as early as possible, but not before the 12th hour of life", but no further detail is provided about exact timing of introduction of feeds or the rate of increase in the two study groups. Müller-Egloff et *al* also showed slower progression of feeds in infants with severe prenatal Doppler abnormalities in infants who received minimal enteral feeds of 18-16ml/day of breast milk or diluted preterm formula from the first day of life and where feed intolerance was defined as gastric residuals of > 3ml or 50% of feeding volume, whichever was greater[94 250]. Mihatsch studied a group of growth-restricted infants and found no differences in the age at starting feeds, time to achieve full feeds or the age at full feeds[251]. However, in this study, initial enteral feeds were of glucose 5% in the first hours of life, with milk feeds started only when the infant had passed meconium, according to the NNU's protocol for feeding all VLBW infants. Prenatal umbilical Doppler studies were performed in only 55% of infants; where these were abnormal or there was brain sparing, feeds were started later. The authors concluded that no special feeding protocol for growth-restricted infants was necessary. Murdoch *et al* performed postnatal Doppler studies of the SMA on the first postnatal day in 64 infants and demonstrated a positive association between NEC, which occurred in 10 infants, and high-resistance flow in

the SMA[252]. In this study, enteral feeding was delayed by 5-7 days in infants who had AEDF or REDF on antenatal Doppler studies.

The uncertainties that exist with respect to enteral feeding in growth-restricted infants are similar to those for appropriately grown preterm infants. However, the observation that IUGR infants seem to be at special risk of developing NEC, together with evidence that gut perfusion may be disturbed postnatally in these infants has made many clinicians feel that enteral feeding may play an even more significant part in either reducing or increasing this risk. The research studies described above illustrate the range of strategies that may be adopted in feeding these babies in the absence of conclusive evidence. In a review article, Dorling reports results of a survey of hospitals in two English health regions, which showed marked variation in clinical practice in commencing enteral feeds and suggested that abnormal antenatal Doppler studies made delaying feeds more likely[96]. The Abnormal Doppler Enteral Prescription Trial[253] conducted in the UK, completed recruitment in 2009. This trial randomised babies born at up to 34 weeks of gestation, in whom antenatal Doppler studies had shown AEDF or REDF, to start enteral feeds "early", on day 2 of life or "late" on day 6 of life. The primary outcome measures are the age at which full feeds of 150ml/kg/day are sustained for 72 hours or more and NEC. It is anticipated that the results of this important and large randomised trial will clarify which of these regimens is preferable in these infants. However, the trial does not address the question of whether the introduction of feeds the first day of life is appropriate in such infants, although it is likely that some clinicians use this approach with MEN. In addition, given the inconsistent availability of Doppler studies in many centres, uncertainty will remain as to whether results of this trial are applicable to growth-restricted infants in whom results of Doppler studies are not available or in those where results have not shown absent or reversed end diastolic flow.

3.4.4 Umbilical vessel catheterisation

Catheterisation both of the umbilical vein and artery are common practices in neonatal care. The insertion of indwelling umbilical catheters in high-risk preterm neonates facilitates monitoring of physiological parameters, administration of fluids and PN and minimises the need for invasive blood sampling. Cochran *et al* first documented both benefits and complications in 1968[254]. However, the use of such techniques has been controversial for many years because of reports suggesting an increased incidence of NEC in babies with

umbilical catheters in place. There are two positions considered acceptable for the placement of the tips of umbilical arterial catheters (UACs). "High" catheters are usually placed so that the tip lies in the descending aorta above the diaphragm and below the left subclavian artery. Low catheter tips lie above the aortic bifurcation and below the renal arteries.

Uncertainty has existed about the risks associated with placement of the catheter tips, duration of use and the concurrent administration of feeds via the enteral route. Many reports documenting these concerns about the use of umbilical catheters date back to the period when exchange transfusion was regularly and often repeatedly performed via the umbilical vein in neonates with haemolytic disease due to rhesus incompatibility. At this time, umbilical venous catheters (UVCs) were placed without radiological confirmation of optimal placement. Castor *et al* described spontaneous gut perforation in two mature infants following exchange transfusion and speculate that altered haemodynamics, together with local bowel wall factors may be contributing factors[255]. Touloukian *et al* described further cases of babies with clinical signs of enterocolitis after exchange transfusion and, in the same paper, also reported an experimental piglet model of exchange transfusion using umbilical catheters, documenting a dramatic rise and fall in portal venous pressure with the potential to lead to angiospasm[256]. Both authors noted the similarity of clinical and histological features in these babies to those in preterm infants with NEC and postulated that aetiological characteristics may be shared by the two conditions that may include complications of UVC use[255 256]. Both also noted the tendency for UVCs to be placed inadvertently within the portal vasculature, increasing the likelihood of associated haemodynamic, thrombotic, embolic or septic complications.

A later study explored the effects of UACs on mesenteric blood flow in 12 clinically stable infants using duplex Doppler sonography [257]. These researchers showed a significant increase in blood flow in the coeliac trunk on removal of the catheters, although there was no evidence of thrombosis having occurred. They suggested that the presence of an UAC might produce obstruction to the coeliac trunk and SMA, lending support to the hypothesis that catheters increase the risk of NEC by reducing mesenteric blood flow in neonates. They therefore recommended caution in the use of UACs in haemodynamically unstable newborn infants.

Wigger, in 1970, reported the post mortem finding of significant thromboses in infants with arterial (n=20) and venous (n=11) umbilical catheters[258]. These infants had serious sequelae

such as pulmonary embolus, hepatic and renal infarctions and in some cases death was directly attributed to catheter-related pathology. Tyson later reported even higher rates in a larger population of infants with UACs sited above the diaphragm[259]. Thirty-three infants of 56 that had UACs were found to have multiple thrombotic lesions in the aorta, representing an increased risk of embolic damage to abdominal organs and 23 infants had mesenteric thromboembolism. No infant without a catheter had thromboses, but in those with catheters, thrombus formation was seen as early as 12 hours after inserting the catheter and the extent of the disease increased with prolonged duration of catheterisation.

Bunton *et al* explored the hypothesis of umbilical catheterisation as a contributing factor to the development of NEC in an epidemiological study[260]. They retrospectively reviewed medical records of 17 infants with NEC and 45 control infants, matched for time of admission, birth weight and the presence of haemolytic disease in 5 infants diagnosed with NEC. Their analysis revealed that the presence of umbilical catheters, duration of use of the catheters and frequency of catheter-related complications were all significantly increased in infants who developed NEC. In infants receiving exchange transfusion, they did not show any difference that could be attributed to the procedure. The authors were cautious about directly attributing NEC to umbilical catheterisation, since NEC did not develop until 2-29 (mean 13) days after removal of the catheters. Of note, also, is the fact that this group was a small and heterogeneous group of infants, with widely varying gestational age and birth weight. Only 5 (29.4%) infants studied were of very low birth weight (<1500g) and a further 7 (41%) were of a gestational age of ≥35 weeks suggesting that predisposing factors to disease may have varied within the group. Others have demonstrated an association between umbilical catheterisation and NEC. Smith *et al,* in a study of 17 infants with NEC and 49 controls showed that 35% of infants with the disease, compared with only 6% of controls had an UAC in situ ($P<0.01$)[261]. However, this group was similarly heterogeneous in terms of birth weight, gestational age and underlying pathology. In a larger study, Palmer *et al* reported on cases of NEC identified in the UK in 1981 and 1982 as part of a UK surveillance scheme comprising eight centres [4]. Sixty-two cases and 97 controls were included. Logistic regression analysis showed an independent effect associated with catheterisation of the umbilical artery, but not the umbilical vein. The associated relative risk was estimated as 18.1 in infants with birth weight <1500g, independent of the effect of birth weight. However, umbilical catheters are most commonly used in infants with respiratory disease and on further analysis, its association with NEC was not independent of respiratory distress in these infants.

Other epidemiological studies have failed to find any relationship between umbilical catheterisation and NEC[8 71 72 74 77 245 262]. The most recent epidemiological study of association was a retrospective review by Guthrie *et al* of an administrative database comparing infants who did and those who did not develop NEC[75]. Univariate analysis showed the use of both umbilical and venous catheters to be significantly related to NEC, but when closer examination with multivariate analysis including birth weight was performed, the effect was no longer present and there was an apparent protective effect of umbilical catheterisation. The authors were unable to provide any explanation of this finding and indeed it is difficult to think of any plausible reason why this effect should be seen.

Later studies have focused on the group of infants known to be at highest risk of NEC by virtue of their low gestational age and birth weight. It therefore appears likely that earlier studies demonstrating a significant relationship were subject to error due to small numbers and heterogeneous study groups. It is possible that the findings may be more related to relatively high numbers of mature infants undergoing exchange transfusion in these studies and misplacement of the catheters with ensuing haemodynamic complications causing an ischaemic effect on the bowel. In recent years, the necessity of exchange transfusion has decreased substantially due to advances in antenatal care and the ability to provide intrauterine transfusion in foetuses with severe haemolytic disease. In addition, it is now routine practice to ascertain catheter positions radiologically prior to using umbilical catheters to withdraw blood or infuse fluids, so it is unlikely that this finding will be replicated in any future studies to identify risk factors for NEC.

A number of researchers have conducted studies to determine the optimal placement of umbilical catheters to avoid potential complications. A Cochrane Review of this subject was published in 2000[263], including five studies[264-268]. Four of these were randomised controlled trials[265-268]. All studies reported on the incidence of NEC, but it was a rare outcome with reported rates of only 3.9% with high catheters and 2.9% with low catheters, which did not represent a statistically significant difference between the groups on meta-analysis. However, Barrington comments that, although this does not necessarily mean that there may not be a clinically significant effect, given the low incidence of NEC overall, it is unlikely that further studies will be performed with sufficient power to detect a clinically significant difference[263]. In this meta-analysis, duration of usage was improved and vascular complications reduced with high catheters, leading to the recommendation that high

catheters should be preferentially used where possible.

The fact that almost all infants who develop NEC have started enteral feeding prior to the onset of disease has led particularly to caution in introducing enteral feeds in the presence of an umbilical catheter. However, there have been surprisingly few studies specifically focusing on this aspect of clinical practice. Lehmiller and Kanto first explored the relationship between umbilical catheterisation, thrombotic disease, enteral feeds and NEC in 1978[269]. In this study of 30 post mortem examinations, mesenteric thromboembolism, apparently caused by umbilical catheters, were seen in 12 of 16 infants with NEC. Ninety-four percent of these infants had been fed enterally before developing NEC. Although the authors found significant relationships between thromboembolism and NEC and between feeds and NEC, there was no statistically significant association between enteral feeds and thromboembolism, except in those infants who had received enteral feeds whilst a UAC was in place. They hypothesised that thrombus caused by the UAC formed intermittent emboli, which were then increased in the presence of increased postprandial blood flow associated with milk feeds. Moreover, they suggested that the effects of ischaemic damage caused by this mechanism would then be exacerbated by the increased metabolic demands of processing feeds in the gut. These findings supported a hypoxic-ischaemic cause for NEC and might explain the increased risk associated with feeding.

Only one clinical trial has since examined this issue. Davey *et al* randomised preterm infants with UACs placed in the low position to receive feeds while the catheter was in place (n=29) or after it had been removed for 24 hours (n=31)[198]. They found no increased risk of NEC or other morbidities in the early feeding group and these infants required PN and percutaneous central venous catheters for shorter periods of time, potentially reducing their risk of systemic sepsis. They concluded that there appeared to be no disadvantage to feeding stable preterm infants in the presence of a low-positioned UAC. However, since NEC is a rare event, this study would have been grossly underpowered to detect a difference had NEC been chosen as a primary outcome measure. Instead, they chose more common, but much less specific, signs of feeding difficulties necessitating discontinuation of enteral feeds as outcome measures representative of NEC risk. Since such feed intolerance is non-specific and may be associated with other illnesses as well as NEC, this may not be the most appropriate approach in a small study.

In 2003 Tiffany *et al* published results of a survey in the USA investigating NNU practice with respect to concurrent use of umbilical catheters and enteral feeds and perceptions of complications associated with this approach. NEC was highlighted by 18% of respondents as a complication related to UVC use[270]. Thirty-seven percent reported regular practice of some feeding with a UVC, 51% some of the time and a further 12% never practised this. Less common was the practice of more complete enteral feeding with a UAC in place, with 24% regularly and a further 44% sometimes doing this. With respect to UAC placement and concurrent feeding, small feed volumes would be given most of the time by 30%, some of the time by 49% and never by 22%. Complete feeding and concurrent use of a UAC was never practised by 49% of respondents. NNUs that never initiated enteral feeding with umbilical catheters in place reported waiting around 12 (0-24) hours after removal of the catheter before starting feeds. The brief structured questionnaires in this survey were sent to NNU directors to obtain a representative response from each unit. The response rate was 70% and no attempt was made to elicit reports of variation between clinicians within any single unit. It is possible that, had this been explored, the range of responses might have been more varied. A further survey was conducted in Australia in 2004 designed to document feeding practices[190]. 56 neonatologists, representing a response rate of 70%, completed this survey. Almost 18% responded that a UVC should be removed prior to starting enteral feeding and 23% would remove a UAC prior to feeding. 67.9% and 66% respectively disagreed with this approach and 10-14% of respondents were uncertain.

Despite conflicting results and limitations of many of the studies considering umbilical catheterisation and NEC, their influence on clinical practice can be seen. Current recommendations are that UVCs should be placed in the inferior vena cava and UACs in the high position. However, the optimum duration of use to minimise complications remains uncertain. The use of both UVCs and UACs remains controversial, particularly when considering the importance and safety of feeding whilst maximising benefits associated with catheter use and the relationship between catheters and NEC remains unproven. It is likely that there is substantial variation in the interpretation of the available evidence on this subject and probable that this is reflected in varying clinical practice.

3.4.5 Blood Transfusion

Anaemia is common in premature infants in part due to the well-recognised anaemia of prematurity and exacerbated by the need to perform repeated blood sampling for

investigations to monitor these infants whose total blood volume is small. Neonates frequently receive multiple blood transfusions, both in the early days or weeks after birth and later when, although their clinical condition is generally more stable, they may nevertheless become progressively and profoundly anaemic and are sometimes symptomatic from this.

There have been reports linking blood transfusion with the occurrence of NEC. McGrady *et al* noted an outbreak of NEC that appeared to be directly associated with blood transfusion[271]. They reported a cluster of cases and compared with a group of control infants, infants with NEC were significantly more likely to have received a blood transfusion shortly before developing the disease, although they do not specify the length of time between the two events. Their analysis does not implicate early feeding, the use of umbilical catheters or exchange transfusion as risk factors in this epidemic setting, distinguishing their cases from previous reports centred on endemic occurrence of the disease[4 260 261]. They proposed volume homeostatic mechanisms as important potential contributing factors. Bednarek *et al* also examined the relationship between NEC and transfusion practice, finding no association between the two[272]. Importantly, however, this analysis was performed according to centres with differing transfusion policies, rather than individual babies and no reference was made to the timing of onset of NEC or transfusion administration in this study. In addition, although they reported progressively decreasing incidence of NEC across units that were "high, middle and low transfusers", these results may be confounded by the unreported differences in severity of illness in babies receiving transfusions.

Mally *et al* reported an association between transfusion and NEC in a group of preterm infants who had progressed from the acute stages of their prematurity-related illness to a more stable condition where care is centred mainly on feeding, growth and preparation for hospital discharge[273]. Anaemia of prematurity can be a significant problem in such babies and transfusions continue to be commonplace, even in the absence of acute illness. They noted a high rate of severe NEC in these babies and chose to examine risk factors in all babies with NEC during a 17-month period. During this time the overall rate of NEC in the NNU was 1.8% and in infants <1000g was 10%. Six cases developed within 48 hours of blood transfusion in otherwise stable neonates and 11 cases developed that were not closely temporally related to transfusion. The median intervals between transfusion and onset of disease were 19 (range 12-38) and 180 (range 96-312) hours respectively. Infants who developed NEC following transfusion were all fully fed on enteral feeds compared with 9% in the non-transfusion associated group, and had no central vascular catheters, in contrast to

91% of the non-transfusion group who had catheters in place. None of the recently transfused infants, but 45% of those who had not recently been transfused was ventilated. These factors and the later onset of disease (32±7 compared with 11±7 days of life) lend credence to assertion that these infants were clinically stable prior to transfusion. All received their transfusions electively for anaemia of prematurity. The NEC in the recently transfused babies was particularly fulminant with pneumatosis intestinalis developing in all, compared with 70% in the other group and mortality was 50% compared with 35%. The authors discuss possible mechanisms to account for this phenomenon and suggest that factors concerned with storage of blood for transfusion may play a part. Red blood cell characteristics may be altered with storage, making them less deformable and hence more susceptible to trapping in the microcirculation, which might give rise to vascular lesions; oxygen transfer capacity may also be reduced, potentially leading to hypoxic injury. Factors within the infants themselves may also play a part and it is of note that all were anaemic; although there was no overt difference between the groups in occurrence of apnoea, the authors suggest the possibility of occurrence of low-grade gut ischaemia that might be exacerbated by repeated mild apnoeic episodes related to anaemia. They conclude that their study did not provide sufficient information to determine a cause for transfusion related NEC, and that it is likely that several factors may be responsible, related both to the infant and to the transfused blood itself.

In the light of suspicion that gut disease may be precipitated by blood transfusion, opinion has varied about whether feeding during transfusion might worsen the risk. A recent study by Krimmel *et al* sought to examine the influence of blood transfusion on mesenteric blood flow in the presence and absence of enteral feeding in 22 preterm infants born at 25 to 32 weeks of gestation[274]. All were receiving enteral feeds of at least 60ml/kg/day. The normal postprandial response is an increase in mesenteric blood flow and blood flow velocity. Doppler flow studies of the SMA were performed sequentially pre-feed and post-feed, before and after blood transfusion in two groups of infants randomised either to have feeds given or withheld during transfusion. Infants who had previously had NEC and those experiencing feed intolerance at the time of the study were excluded and the study group was stratified by weight of above or below 1250g. Those of higher weight were transfused later in life and for a lower level of haemoglobin than larger babies. Doppler studies in infants >1250g showed an increase in peak and mean blood flow velocity in response to feeding when anaemic, but not after transfusion. This effect was not seen in smaller infants who displayed no response to feeding prior to transfusion. Following transfusion, neither group

exhibited a change in blood flow in response to feeding. The authors hypothesised that larger infants may be at greater risk of NEC secondary to transient gut hypoperfusion post transfusion. The study found no difference between the groups based on whether they were fed during transfusion, or whether feeds were of breast milk or formula and the authors interpret these findings as indicating that feeding during transfusion is probably a safe practice. However, since the study was not designed to investigate NEC as an outcome measure, cautious interpretation and extrapolation of these results to clinical practice is required. Nevertheless, this recent work by Krimmel supports the observations made and hypothesis suggested made by Mally *et al* that larger and more mature infants with anaemia of prematurity may be more vulnerable to the haemodynamic effects of transfusion, putting them at an increased risk of NEC[273].

In the absence of clear recommendations, practice relating to blood transfusions has been extremely diverse and results of clinical studies and trials examining practice have been conflicting. Bednarek *et al* highlighted significant variation between NNUs in an observational study of six centres[272]. This variation was not related to case mix in terms of birth weight or severity of illness of babies included. Bell *et al*, in a randomised trial including 100 infants, attempted to clarify whether transfusion practice according to haemoglobin levels should be restrictive (transfusing at lower levels of haematocrit) or liberal (transfusing at higher levels of haematocrit)[275]. Results showed an increase in the number of transfusions in the liberal group, but a greater incidence of adverse neurological outcomes in the group transfused at lower levels.They concluded that a more liberal transfusion policy may be more appropriate. A similar randomised controlled trial in more than 400 infants with birth weight of <1000g did not support these findings. In this study, Kirpalani *et al* showed little evidence of benefit in using a restrictive policy based on haemoglobin levels during the whole of the neonatal hospital stay, but found that these infants received significantly more transfusions, which might theoretically increase risks of transfusion-related complications[276]. They showed no difference in secondary outcomes of the trial, including NEC and concluded that a restrictive policy was equally effective and did not increase morbidity. Their follow-up of 93% of the original cohort at 18-21 months did not show any difference in a composite outcome of death and neurodisability[277]. However, post hoc analysis revealed worse cognitive outcomes in the restrictive group (P=0.016), lending some support to the view that the more liberal approach of transfusing at higher haemoglobin levels may be more beneficial, although cautious interpretation of unplanned post hoc analyses is advisable. Failure to define clearly a preferred strategy means that there

may still be considerable variation in opinion and practice. There is clearly a need for further research to define safe levels at which infants should be transfused and elucidate the factors that may link blood transfusion and NEC particularly in more mature very low birth weight babies in order to guide clinical management and optimise transfusion strategies. There has been no recent documentation of current transfusion practice or its relationship to the development of NEC.

3.4.6 Patent ductus arteriosus (PDA) and its management

The relationship between the presence of PDA, its management and the development of NEC has been discussed for many years. PDA is often seen in sick preterm neonates and NEC is also commonest in this group, so the two conditions are likely to occur together. The presence of a PDA has been suggested as a risk factor for NEC, with the likely mechanism being the flow of blood from mesenteric arteries into the aorta and through the PDA, leading to reduction of perfusion in the intestine. Recent research in preterm baboons showed that the presence of a PDA limited the ability of the animal to increase blood flow to the intestine postprandially, supporting this theory[278]. However, none of these animals developed NEC. Van de Bor *et al* found that in a cohort of over 1300 babies <32 weeks or <1500g birth weight, the incidence of PDA was 10.7%, and those with PDA were more likely to develop NEC than those without PDA, even after adjustment for gestational age and birth weight[279]. A later study also showed PDA to be an independent risk factor for the development of NEC[280]. Milner showed that NEC in the presence of a PDA was associated with higher rates of mortality[281]. Treatment of PDA might therefore be reasonably expected to reduce the incidence of NEC in these babies. Two methods of treatment are currently available: surgical ligation or medical treatment with a cyclooxygenase inhibitor, most commonly indomethacin. Each of these treatments carries risk. Surgical management may be complicated by problems with anaesthetic administration, intra-operative difficulties or post-operative haemodynamic instability or infection. Medical closure of PDA is often attempted first if therapy is deemed necessary. However, indomethacin has been associated with renal impairment, hyponatraemia, thrombocytopenia, spontaneous intestinal perforation and gastrointestinal bleeding. Indomethacin use has also been associated with an increased risk of NEC. It is known to reduce mesenteric blood flow and it is suggested that, in the presence of a PDA, indomethacin may further compromise perfusion of the bowel[282 283]. A systematic review of randomised controlled trials, performed in 2002, was unable to demonstrate an

increased risk of NEC with the use of prophylactic indomethacin in preterm infants[284]. However, most of the studies included in this review were small and confidence intervals were wide for the results; however, the largest randomised trial to date showed no difference in the incidence of NEC with prophylactic therapy[285].

Although prophylactic indomethacin confers some short-term benefits, no long-term beneficial effects have been demonstrated and this strategy has not been widely adopted, with indomethacin now more usually given for treatment of PDA that is thought to be haemodynamically significant. Grosfeld *et al* examined the rates of NEC in a group of babies with significant PDA treated with indomethacin[286]. 35% developed NEC, compared with 13% in infants without PDA. Rates of perforation were also higher and both findings were statistically significant. However, the two groups of infants were matched only for birth weight and gestation and it is possible that other differences, particularly in severity of illness, might have contributed to the difference in findings. Since the condition of SIP has relatively recently been identified as a separate entity from NEC then it may be that some of the increased rates of perforation were as a result of this, rather than more severe NEC. The authors do not discuss this. Fujii performed a retrospective study in 65 infants <27 weeks of gestation and birth weight <800g[287]. Infants were treated for PDA either prophylactically or after 48 hours of life, when it became clinically significant. In this study, the rates of NEC were similar with early or later treatment, but the group receiving prophylaxis had a significantly increased rate of perforation. They speculate that this may have been caused by high rates of antenatal steroid administration resulting in increased prostaglandin synthase inhibiting effects due to the drug combination. In contrast, O'Donovan, also retrospectively reviewed records of 224 very low birth weight infants treated for significant PDA with either indomethacin, surgical ligation or both[288]. The incidence of NEC was similar in all groups; SIP was reported separately and was also similar between the groups. Dollberg, in a population-based study, found that although PDA was an independent risk factor for NEC, this risk was not increased by the use of indomethacin therapy[280].

There have been no randomised controlled trials addressing the question of optimum management of PDA. In the absence of this evidence, medical treatment, surgical ligation and no treatment probably lie within the boundaries of current clinical practice. Conflicting study results and small study sizes limit interpretation of the possible effects of different management strategies on the incidence of NEC. In view of the perceived close link between enteral feeding and NEC, it is likely that this too influences feeding practice and anecdotal

reports suggest that some clinicians manipulate feeds differently either because of the presence of or treatment for PDA. The effects of feeding during treatment with indomethacin have not yet been determined.

3.5 Feed tolerance and feeding methods

Underpinning the issue of achieving full enteral nutrition in preterm neonates is the need to attain adequate nutritional volumes of milk. It is clear that a very preterm baby's gut is not sufficiently mature to be able to deal with full enteral feeding from birth and evidence is conflicting about how best to achieve this in the safest, but quickest way. Whether or not a baby's feeding progresses satisfactorily may be related to a large number of factors, many of which have been previously discussed. Others may relate to the method by which the feed is administered. There is still little to guide clinicians wishing to determine whether their chosen feed strategy and feeding method is correct for an individual baby. Regular assessments of the baby's clinical condition and abdominal examination may alert the attending neonatologist to obvious or imminent gastrointestinal pathology. However, it may be considerably more challenging to determine whether a baby is "content" with the rate at which feeding is progressing, or whether larger or smaller volumes may be more appropriate. The terms "tolerance" and "intolerance" of feeds are frequently used terms to attempt to describe this, yet definition of either is difficult.

3.5.1 Gastric residual volumes

In preterm neonates establishing enteral feeding in the first weeks of life, it is common for gastric residual volumes to be assessed prior to feeding. Contents of residual volumes include milk from previous feeds, saliva and gastric secretions. In babies who do not have abdominal signs suggestive of pathology, the amount and colour of residual volumes are often used as a measure of feed tolerance. Increased residual volumes aspirated from the stomach before a feed are often regarded as a sign of intolerance or as an early sign of gastrointestinal disease such as NEC. On the basis of these gastric residuals, feeds are temporarily discontinued in an attempt to avert or minimise the consequences of NEC, should it develop. If NEC does not ensue, then feeds are restarted some time later. This is

perceived as safe feeding practice, yet for an extremely small baby, multiple or prolonged omission of feeds may represent significant reduction in nutrition.

Malhotra studied gastric residual volumes in 50 healthy preterm babies, some of whom received PN to supplement milk feeds[289]. Gastric residual volumes decreased during the first week of life as feed volumes increased and were less in babies placed prone (24.2 ±10.2%), than in those lying in the supine position (12.8 ± 4.3%). Mean gastric residuals were less in babies receiving a greater proportion of their feed via the enteral route, supporting the findings of others that enteral feeding enhances gut motility. This study found no difference in gastric residual volumes between infants fed human or formula milk. Mihatsch *et al*, within a randomised controlled trial of infant formulas, studied the relationship between the volume and colour of gastric residuals and feeding tolerance in 99 extremely low birth weight infants in the fist two weeks of life[290]. Infants were fed every two hours with human milk where available or formula starting at 12ml/kg/day and increasing by this amount daily if the infant had received >50% of the daily volume in the previous 24 hours. Specified gastric residual volumes were regarded as acceptable for different birth weights: ≤750g, up to 2ml; 751-1000g, up to 3ml. Where volumes were less than specified, the full feed was given; where residual volumes were greater, the feed volume given was made up to that of the intended feed volume; where residual volumes exceeded the feed volume, milk was withheld. Feeding was not influenced by hypotension, mild abdominal distension, infection, indomethacin therapy or the colour of the residual. 59 infants advanced feeds according to the study protocol. There was no relationship between the mean residual volume and feed volume at 14 days. Most residuals were milky in colour and green or bloodstained residuals did not influence feeding volumes, in the absence of other clinical signs. The authors suggested that residual volumes of <2-3ml did not indicate feed intolerance. No increase in residual volumes was seen infants developing NEC. In a further study by the same research group, gastric residual volumes of up to 5ml/kg were tolerated without adverse effects[168]. Cobb used a case control study design in 51 VLBW infants to compare residual volumes in infants with and without NEC[291]. Each case was matched with 2 controls that had never had feeds withheld for more than one day. The total residual volumes as a percentage of total feed volumes were increased in NEC cases compared with controls and the maximum residual volumes were increased prior to development of NEC. There was a non-significant trend to lower total feed volumes in the NEC group after 6 days of feeding, suggesting worse feed tolerance. The authors suggested that residual volumes of >3.5ml or 33% of the feed volume may be associated with an increased risk of NEC. However, controls were selected

because they had not shown feed intolerance. This choice may have excluded many babies who experienced feed intolerance for other reasons, yet did not go on to develop NEC and the effect of this would be to exaggerate the differences between the groups, making interpretation of the results more difficult. In addition, the use of total residual volumes is not helpful for clinical practice, where decisions must be made based on the day-to-day feed tolerance of babies. Bertino recently published results of another case control study including over 800 infants[292], accepting residual volumes as suggested by Mihatsch *et al*[290]. The overall incidence of NEC was low (2.2%). Mean maximum residual volumes were greater in infants with NEC and the percentage of haemorrhagic residuals was greater, but percentage of bile-stained residuals was similar between the groups. Although larger volumes were noted in cases of NEC, this study did not attempt to quantify a volume at which residuals may predict NEC, but Bertino suggested that early bloodstained residuals might be important. Neu and Zhang, in a review article, suggest factors that might indicate feed intolerance and increased risk of intra-abdominal pathology[293]. With respect to gastric residual volumes, they suggest that volumes of >3ml/kg should prompt consideration of temporary discontinuation of feeds pending further assessment.

Another area of recent work is investigation of the role of amylin, a potent inhibitor of gastric emptying, in feed intolerance. Kairamkonda *et al* showed that serum amylin is increased in preterm infants with feed intolerance compared with those tolerating increasing feed volumes[294]. However, gastric emptying was not measured in these infants. This work is in its infancy and confirmation of these results and mechanisms is necessary. However, it is possible that with time, this will represent a measurable indicator of feed intolerance in preterm infants.

Currently, there is no established guidance about the assessment of feed tolerance, although most clinicians accept that gastric residual volumes are probably the best measure available at present. Further research is required to elucidate the relationship between gastric residual, their type and volume, feed tolerance and the development of NEC. Until such information is available, it is likely that clinical practice will encompass widely ranging differences. There are no published data documenting the gastric residual characteristics on which clinicians base their decision-making with respect to temporary discontinuation of feeds.

3.5.2 Continuous or bolus feeding

Preterm infants require a period of nutritional support using tube feeding before they become mature enough to take suck feeds, either from the breast or bottle. Feeds may be given either as intermittent bolus feeds or as continuous feeds. Both are associated with theoretical risks and benefits. Intermittent bolus feedings are considered more physiologically appropriate, as they promote cyclical surges of gut hormones needed for gut maturation[295]. Conversely, delayed gastric emptying in the preterm neonate may render the babies less able to cope with larger gastric volumes of milk[296].

Toce alternately assigned 53 babies <1500g to continuous or intermittent 3 hourly nasogastric feeding for a minimum of 7 days until transfer to another unit, establishment of suck feeding or a maximum of 28 days[297]. Feed intolerance was defined as suspicion of NEC, increased gastric residuals or withholding of feeds for 16 hours or more. Feeding method did not predict changes in head circumference, total protein level or bilirubin level. Continuous feeding was associated with increased weight gain in infants with birth weight of 1000g-1249g, but not in heavier babies. Three infants experienced more than 3 episodes of feed intolerance or NEC (2 continuous; 1 intermittent) and were regarded as study failures. In this study, intermittently fed infants had a non-significant increase in apnoeic episodes. Continuously fed infants had a slight increase in feed intolerance, which reached significance only in babies of 1000g-1249g. However, numbers were small and infants achieving suck feeds before 7 days were excluded from analysis. Since these infants presumably tolerated feeds well, this may have artificially exaggerated problems in the remaining group. Akintorin also observed more apnoeic episodes in intermittently fed babies and increased residuals in those fed continuously but overall feed tolerance did not differ between the groups[298]. Silvestre compared feeding methods in 82 VLBW infants and found comparable weight gain, head circumference, time to reach full enteral feeds and length of hospital stay between the groups[299].

In a randomised trial of gut priming in 171 infants (gestational age 26-30 weeks), Schanler also compared continuous and intermittent feeding[182]. This study found significantly less feed intolerance, defined as increased gastric residuals, and increased weight gain associated with intermittent feeding. Dollberg also found 2-3 hourly intermittent feeding to be superior to continuous feeding in a randomised trial of 28 infants, a result which was contrary to their

original hypothesis[300]. Infants tolerated continuous feeds less well and took significantly longer to reach full feeds (P <0.03).

In contrast, other studies have found continuous feeds to improve outcomes. Rojahn, in a retrospective analysis of records of 45 VLBW infants, found that babies attained full feeds of 120 or 150ml/kg/day more rapidly when fed continuously, and attributed this to larger volumes being tolerated in this group during the first few days of life[301]. Dsilna *et al* randomly assigned 70 infants <1200g and 24-29 weeks of gestation to continuous or intermittent feeds[302]. Continuously fed infants achieved full enteral feeds earlier than bolus fed infants and this effect was most marked in the smallest infants <850g.

A systematic review of all studies was unable to detect a difference between the two methods of feeding in terms of time to full enteral feeds, but was unable to reliably assess risks and benefits that may be associated with either method from the data available[303]. In all studies considered, intermittent enteral feeds were given every three hours. It is possible that more frequent bolus feeding may have different effects and that infants may display different tolerance to feeds depending on the interval between them. Given the lack of evidence for superiority of one method of feeding over another, it is likely that clinical practice is based on personal preference and policies in NNUs. There are no published data indicating which method is most commonly used in current practice or how frequently bolus feeds are given when this method is used.

3.5.3 Nasogastric or transpyloric feeding

In view of the delayed gastric emptying in preterm infants, it has been suggested that feeding directly into the upper bowel may improve feed tolerance and ensure more reliable delivery of milk feeds into the area where absorption takes place. In addition, nasojejunal feeding may reduce the risk of reflux through the gastro-oesophageal valve and its potential complications, the most serious of which is milk aspiration.

Rhea and colleagues first described their experience with transpyloric feeding of infants, including preterm neonates in 1973[304]. They found no evidence of gastrointestinal or surgical complications and concluded that it was a safe and easy method of feeding. Cheek and

Straub, in the same year, reported a study of 10 term and 36 preterm neonates who were fed by this method without serious complications[305].

Wells and Zachman first compared transpyloric feeding with nasogastric feeding in 18 VLBW infants, alternately assigned to the each method. Transpyloric feeds were given continuously and nasogastric feeds every 3 or 4 hours. They encountered no problems and found that infants fed via the nasojejunal route had faster initial weight gain, regaining their birth weight earlier than nasogastrically fed infants[306]. Van Caillie and Powell studied 11 VLBW infants comparing continuous nasogastric and nasoduodenal feeding[307]. Transpyloric feeding resulted in higher caloric intake during the first week of life and earlier regain of birth weight. Two episodes of aspiration occurred and both babies had their tubes placed in the stomach at this time. The authors suggested that transpyloric feeding might be most appropriate in the first two weeks of life.

However, subsequent studies have urged caution. Roy *et al* compared feeding methods in 18 healthy infants[308]. Both were tolerated well, but over half of the nasojejunal group were found to have gastric residual volumes, suggesting reflux through the pylorus. There were no significant differences in gain in weight or head circumference between the groups, although there was a trend favouring nasogastric feeding. Stool frequency was increased with nasojejunal feeding, as was stool fat content, raising concerns of possible decreased absorption. A larger study of 44 infants found difficulties in passing nasojejunal tubes on many occasions and no benefits from nasojejunal feeding, but infants fed by the nasogastric route had higher calorie intake[309]. One infant in the nasojejunal group died following aspiration and two following NEC, compared with only one death in the nasogastric group from NEC. They concluded that possible risks of using transpyloric feeding outweighed evidence of benefit. Pereira[310], Laing[311] and Macdonald[312] also found greater complexity, more complications and no significant benefits with transpyloric feeding compared to nasogastric feeding. Complications of transpyloric feeding were extra radiation needed to check tube position, aspiration and gastric bleeding. Systematic reviews of the randomised trials comparing transpyloric versus gastric tube feeding in preterm infants found more adverse effects and no benefits with transpyloric feeding and the authors were unable to recommend this practice over gastric feeding.

In a retrospective review, the role of transpyloric feeding has recently been investigated in apnoea associated with gastro-oesophageal reflux in preterm infants[313]. In 15 infants,

transpyloric feeding was initiated at between 20 and 51 (mean 32) days of age for symptoms associated with reflux. Twelve of these responded with a reduction in apnoeic episodes. A further retrospective study also showed a reduction in apnoea and bradycardia thought to be associated with gastro-oesophageal reflux[314]. Without a control group, and given the spontaneous improvement in apnoea of prematurity with increasing age, it is not possible to be sure that improvement was related to this intervention. However, transpyloric feeding may have a role in reflux disease in older preterm infants and this warrants further exploration.

Review of this evidence suggests that routine use of transpyloric feeding in preterm infants is inherently more complex and may be associated with complications not seen with nasogastric feeding. In addition, ascertainment of nasojejunal tube position may require significantly more x-ray examinations. Anecdotal reports suggest that it is used currently in NNUs, either routinely or in selected babies for management of refractory feed intolerance or gastro-oesophageal reflux, although this has not been documented.

3.6 Gastro-oesophageal reflux in preterm neonates

Gastro-oesophageal reflux (GOR) is common in preterm infants; they lie horizontally, take in relatively large quantities of milk feeds and have an immature, lax oesophageal sphincter. Dhillon and Ewer conducted a survey to determine an estimate for the incidence of GOR in preterm infants in UK neonatal intensive care units and found the incidence to be approximately 22% in infants under 34 weeks of gestation[315]. However, they also found that there was considerable inter-unit variation in both diagnosis and management. Indeed, the significance of GOR is contentious issue in neonatal medicine. Many regard it as a phenomenon that is physiological rather than pathological, whereas others believe that it is a cause of significant morbidity. Indicators of reflux include regurgitation of feeds and vomiting and these may, in some cases, be associated with aspiration of milk. Adverse outcomes that have been linked to GOR include apnoea, exacerbation of chronic lung disease, poor weight gain and prolonged hospital stay.

Apnoea occurring around the time of feeding is often attributed to GOR. Early case reports described episodes of respiratory arrest in term born infants at 1-5 months of age, which resolved after surgical treatment with fundoplication and suggested the link with GOR[316].

Herbst observed increased reflux, detected by oesophageal pH monitoring in 14 infants with bronchopulmonary dysplasia (BPD) and recurrent apnoea and proposed an association between GOR, aspiration and chronic lung disease[317]. Menon studied 10 infants with feed regurgitation and showed that apnoea of both short and prolonged duration was more frequent at times of feeding than at other times and concluded that the two were temporally and perhaps causally linked[318]. However, Menon also observed that many regurgitation episodes were not associated with apnoea.

Other researchers have sought to confirm a temporal relationship between GOR and apnoea in preterm infants, using various methodologies. Jolley used 24 hour pH monitoring to determine the occurrence of prolonged duration of reflux during sleep in 82 infants with respiratory symptoms thought to be caused by GOR[319]. They found that this was a less common occurrence in infants below 39 weeks than in those above 39 weeks and concluded that it was probably unrelated to the development of BPD. De Ajuriaguerra found no relationship between apnoea and GOR in a small study of 20 preterm infants using pH monitoring[320]. Peter *et al* studied 19 preterm infants at a mean postnatal age of 26 days using multichannel intraluminal impedance techniques (MII), electrocardiogram, nasal air flow and oxygen saturation monitoring[321]. Two thousand and thirty-nine episodes of apnoea were observed, but the number occurring at times of reflux was similar to the number during periods where infants did not experience reflux. There was no relationship even when reflux reached the level of the pharynx. In a study of 6255 episodes of GOR detected on overnight pH monitoring, Di Fiore and colleagues were also unable to detect a temporal relationship with apnoea[322]. In fact, their results showed a decrease in apnoea in the periods following reflux episodes, possibly due to increased arousal caused by the reflux. They were also unable to show any effect of GOR on duration of apnoeic episodes. Bhat et al also incorporated a comparison between prone and supine positioning in 20 preterm infants with and without BPD at 36 weeks corrected gestational age[323]. There was no difference in the number of apnoeic episodes in the BPD and non-BPD groups, and no relationship between apnoea and GOR in either position.

These conflicting results may at least in part be related to the methods used for monitoring the occurrence of reflux. Although carefully designed, these studies have chosen to use either pH monitoring or the more recent technique of MII. Continuous 24 hour oesophageal pH monitoring has been frequently employed in the diagnosis and investigation of suspected symptomatic reflux. Significant GOR is diagnosed when there is pH <4 for 10% of the

monitoring period. The limitation of this method is its ability to detect only acid reflux (pH<4) and alkaline (pH>7.5) reflux. Frequent milk feeds can buffer gastric acid and raise the pH of gastric contents to a level where this would not be detected on pH monitoring[324] [325]. The advent of MII has made detection of non-acid reflux possible. Electrical impedance changes when fluid or air passes between electrodes at multiple sites, allowing the direction of flow to be determined[326]. Simultaneous pH monitoring and MII can now be performed, allowing detection of both acid and non-acid GOR. Wenzl used this technique in 22 term infants and observed 165 episodes of apnoea in 20 infants, 96% of which lasted for less than 10 seconds[327]. There was an association between GOR and apnoea in this group. Almost 30% of all apnoeas were associated with GOR and one third of all apnoeas were within 30 seconds of an episode of reflux. However, almost 80% of these reflux episodes were non-acidic. Only one published study to date has used this technology in preterm infants. Corvaglia *et al* studied 26 preterm infants ≤32 weeks (range 25-32 weeks) of gestation who were receiving full enteral feeds and experiencing recurrent apnoeic episodes[328]. Using simultaneous pH monitoring, MII and polysomnography, infants were monitored for two 3-hour periods postprandially. Apnoea was considered related to GOR if it occurred within 30 seconds before or after a reflux episode and pathological if it lasted for 5 seconds or more and was accompanied by bradycardia. Reflux was identified on 1065 occasions, 382 by pH monitoring and 683 on MII. Apnoea was identified on 1136 occasions and of these, 154 episodes were related to GOR. The frequency of apnoea during the 1-minute period around the onset of GOR was significantly greater than the frequency during the total period free of GOR. However, there was variability between individual infants, with some appearing to be more susceptible to apnoea associated with GOR than others.

The evaluation of GOR in preterm neonates is fraught with difficulty and differences in practice and opinion are many, in the face of conflicting evidence. Making the correct diagnosis is a challenge in itself, with the most common diagnostic test having recognised limitations and more sophisticated technology having significant resource implications; this in a condition for which there is no agreement about either the clinical significance of the condition or need, efficacy and safety of available treatments. Yet the diagnosis of GOR and the use of pharmacological treatment appear to be common. Responses to the postal survey by Dhillon and Ewer in the UK indicated that non-pharmacological treatments for reflux, such as positioning, were used alone in 54% of units and in 46% drug treatments were also used [315]. A recently published retrospective analysis of 1598 extremely low birth weight infants in the USA reported that 24.8% of them were discharged with medications to treat

reflux [329]. However, there was significant variation in practice between centres, with rates ranging from 2% to 90%. There are no recent published reports documenting the actual, rather than reported use of anti-reflux medications in the UK.

3.6.1 Pharmacological management of GOR and feed tolerance

A number of different pharmacological therapies are used in the management of GOR in neonates. These include feed thickeners, alginates, gastric acid inhibitors and prokinetic agents.

3.6.1.1 Feed Thickeners

Thickening of infant feeds has been advocated for many years. The rationale behind this practice is that the increased weight and viscosity of the feed will prevent reflux of stomach contents into the oesophagus. Various agents have been used, including rice cereal, carob-bean gum, carob-seed flour and sodium carboxymethylcellulose. Most studies have been performed in older infants and young children, rather than in the newborn period and a Cochrane review was unable to identify any randomised trials of the use of feed thickeners in neonates [330]. Studies including preterm infants are even fewer. Since the natural history of GOR is to resolve with maturity and changes in infant posture over time, results of non-randomised trials in older infants should be interpreted with caution. Orenstein *et al* found that vomiting and crying were reduced and sleeping time increased in infants of less than one year of age [331]. However, reflux measured by scintigraphy did not decrease and infants coughed more when fed thickened feeds. In a small, randomised trial of term infants, an "anti-regurgitation" formula containing bean gum decreased regurgitation and reflux on pH monitoring [332]. A further multicentre study in term infants confirmed Orenstein's findings of reduced regurgitation and improved sleep, but observed less coughing in infants fed with a pre-thickened formula [333]. Wenzl *et al* used a randomised crossover study of combined pH monitoring and MII to investigate the effect of feed thickening in a study of 14 healthy term infants (mean age 42 ± 32 postnatal days) [334]. Infants were fed alternately with a formula with or without added carob bean gum. They observed reflux in all infants, with a total of 1183 episodes, of which 32% were acidic, 0.3% alkaline. In keeping with this group's other studies[326] [327], the majority of reflux episodes were non-acid. There were 83 episodes of regurgitation. They found a significant reduction in frequency and amount of regurgitation, principally related to non-acid events. There was no difference in acid reflux.

There are few reports of the use of feed thickeners in preterm infants, although their use may be common in clinical practice [315]. In a letter, Clarke and Robinson reported on two preterm infants who died from NEC, having been treated for non-specific symptoms attributed to GOR. They speculated that thickened feeds may have led to the development of NEC either by causing bowel obstruction and subsequent overgrowth of bacteria or by mucosal injury associated with the high calorie density of the feed [335]. Corvaglia *et al* sought to examine the efficacy of thickened human milk in a crossover study in preterm infants, using combined pH monitoring and MII. They found no reduction in reflux with feed thickening and the study was discontinued after the recruitment of only 5 infants, in view of the suggestion of a link with NEC as proposed by Clarke and Robinson. Although the evidence of an association with NEC is scant and studies examining efficacy of feed thickening few and limited, these authors and others caution against the use of feed thickeners in preterm infants, at least until good feed tolerance has been achieved[335-337].

3.6.1.2 Alginates

The antacid preparation most commonly used for the treatment of reflux in infants is Gaviscon® Infant (Reckitt Benckiser Healthcare [UK] Ltd), which contains sodium and magnesium alginate. Unlike Gaviscon® preparations for older children and adults, which also contain bicarbonate to alter the pH of stomach contents and form a "foam raft" over the stomach contents, the infant preparation probably acts as a feed thickener [338]. Gaviscon has not been extensively studied in neonates and most studies in infants have used preparations available before the introduction of the infant preparation. Buts, in 1987, studied 20 infants and children with GOR and found that reflux measured using 24 hour pH monitoring was significantly reduced after treatment with Gaviscon compared with the placebo group[338]. Forbes *et al* studied the effects of Gaviscon and metoclopramide in a group of 30 patients with wide ranging ages (4 months to 17 years), but found no reduction in reflux episodes with wither treatment [339]. Miller also observed some improvement in reflux in infants recruited in a general practice setting and treated with alginate preparation [340]. These studies reported no adverse effects. However, previous reports have suggested that the use of Gaviscon may be associated with intestinal obstruction caused by bezoars [341 342]. These reports have led to recommendation that it should not be administered concurrently with other feed thickening agents [343 344].

The most recent study used Gaviscon Infant and included 20 patients less than 12 months of age, assessed with combined pH monitoring and MII [345]. Infants were monitored over a 24-hour period during which there were six random administrations of Gaviscon Infant or placebo. The results showed that, although there was a small decrease in reflux in infants treated with Gaviscon Infant, this difference was not statistically significant. However, others have suggested that the period of monitoring may have been insufficient to detect a difference between the treatment and placebo [346]. Although Gaviscon Infant preparations are readily available, they are not recommended for infants of less than one year of age except under the guidance of a medical practitioner. Evidence for either the safety or efficacy of alginates in the preterm population is lacking.

3.6.1.3 Gastric acid inhibitors

Euler *et al* showed that gastric acid is produced during the first hour of life in both term and preterm infants from 33 weeks of gestation[347]. Hyman *et al* characterised the nature of gastric acid secretion in preterm infants[348]. This work showed wide variation in rates of acid secretion between babies, but all demonstrated increasing secretion during the first four weeks of life. This increase appears to be more related to postnatal than gestational age. By six postnatal weeks, all infants were able to maintain a gastric pH of <4.0. Kelly *et al* later demonstrated the presence of parietal cells in the developing stomachs of foetuses and infants between 13 weeks of gestation and 21 weeks of postnatal age, suggesting that mechanisms for gastric acid production may be present from this very early stage in development[349]. Although studies have shown that much reflux in infants is non-acid, positive results from pH monitoring in infants frequently lead to trials of treatment with gastric acid inhibiting medications.

(a) H_2 receptor antagonists

These drugs reduce gastric acid production by inhibiting the H_2 receptors on gastric parietal cells. Ranitidine is one of the most commonly used H_2 receptor antagonists to treat GOR in preterm infants, but has not been studied in randomised controlled trials in this group. In a study of 10 infants treated with postnatal steroid therapy for BPD, ranitidine significantly reduced gastric acidity and the authors suggested that it might be a useful adjunctive therapy in such infants to prevent gastric perforation secondary to steroids. However, the subsequent association of postnatal steroid therapy with later cerebral palsy has substantially decreased the use of this in the management of BPD[350]. A further randomised trial of ventilated infants in neonatal intensive care used prophylactic ranitidine and confirmed the reduction of stress-

associated gastric mucosal lesions[351]. This trial did not report any adverse effects of ranitidine therapy. However, Cothran found that increased gastric pH associated with the use of ranitidine also increased rates of colonisation with pathogenic bacteria compared to control infants who did not receive the drug [352]. Guillet *et al* sought to determine whether this effect on bacterial overgrowth was associated with the development of NEC [65]. This large study included VLBW infants and the rate of NEC was 7.1% overall. They found that both the incidence of NEC and the frequency with which H_2 receptor antagonists were used varied significantly between centres. A case control analysis of 787 infants with NEC and 2357 controls, matched for birth weight, race and centre, showed that the use of H_2 receptor antagonists was significantly associated with an increased incidence of NEC. Limitations of this study included its retrospective design and the lack of information about aspects of feeding practice, such as the use of breast milk and feeding regimens. They were also unable to control for other potential confounding factors, such as the management of PDA. Nevertheless, this study supported previous work showing that acidifying the milk feeds of premature infants >1250g led to reduced bacterial colonisation and reduced incidence of NEC, although this group reported a high (18%) baseline incidence of NEC prior to the study [353]. In the light of this evidence, it has been suggested that avoiding exposure to H_2 receptor antagonists may be important in preventing NEC. A recent report of a retrospective study has also linked an increased incidence of late-onset sepsis with ranitidine use in neonatal intensive care, but this has not been explored further to date [354].

(b) Proton pump inhibitors

Proton pump inhibitors inhibit gastric acid secretion by inactivating the H+, K+ -ATPase pump in parietal cells. Although widely used in adults, this group of drugs has only recently been studied in the neonatal population [355]. Moore *et al* assessed the effect of omeprazole in 64 irritable infants with GOR during the first year of life in a randomised controlled trial [356]. Although reflux was reduced in treated infants, symptoms remained unchanged in both treatment and placebo groups, suggesting they may be coexistent, rather than related [357]. A randomised crossover study in 10 preterm infants, in whom conservative treatment for GOR had been ineffective, used pH monitoring to evaluate the efficacy of omeprazole [358]. This study showed similar results, in that detected reflux episodes were significantly reduced, but in spite of this effect, symptoms of vomiting, apnoea, bradycardia and irritable behaviour persisted. Orenstein chose to investigate lansoprazole in a multicentre double-blind randomised placebo controlled trial including 162 infants, of which 44 were preterm [359]. Identical numbers of infants in each group responded to treatment, in both the overall group

and the preterm subgroup. Lower respiratory tract infections were commoner in the treatment group, but it is possible that other factors, not attributable to lansoprazole may have been important in these infants. Given the increasing evidence that this group of drugs does not affect symptoms commonly attributed to GOR, its use in the management of this condition must be questioned. In addition, neither the safety profile of proton pump inhibitors in preterm infants, nor the long-term effects of treatment have yet been defined. There have been no published reports of any association between proton pump inhibitor use and NEC though, in the absence of evidence, it is possible that similar mechanisms may be implicated in the future as those relating to H_2 receptor antagonists.

3.6.1.4 Prokinetic agents

A small number of prokinetic agents have been used in the newborn. Cisapride was effective in decreasing GOR in preterm infants[360] and was widely used, but the product license for this drug was withdrawn in 2000 because of reports of sudden death due to cardiotoxicity[361]. Since this time, other prokinetics have been used increasingly.

(a) Metoclopramide

Metoclopramide is a dopamine antagonist, which enhances the gut's response to acetylcholine and so increases gut motility and gastric emptying. A number of studies have been conducted in older infants and children, but studies in preterm infants are few and numbers included are small. Results of two small studies in the 1980s reported that symptoms of GOR were reduced with treatment without any increase in adverse effects[362 363]. However, these observational studies included only 6 and 14 symptomatic infants respectively. Kimball and Carlton retrospectively reviewed records of 132 preterm infants treated with either cisapride or metoclopramide for GOR and associated apnoea [364]. In this study, neither drug reduced the frequency of apnoeic episodes; however, the retrospective study design may have precluded the consideration of important confounding factors. A recently published randomised, blinded, crossover trial used metoclopramide and ranitidine in the treatment of bradycardia attributed to GOR in 17 preterm infants[365]. Results showed that infants had significantly less bradycardic episodes during drug treatment than with placebo. In a small study such as this, the finding may represent a type 1 statistical error. However, the side effect profile of ranitidine in adults includes cardiac arrhythmias and the authors suggested this as a potentially plausible explanation. A systematic review has been published on the effects of metoclopramide on GOR in infants, although few preterm infants were included [366]. It concluded that there was insufficient evidence to either recommend or

oppose the use of the drug for this indication. Substantial concern also exists about adverse effects of metoclopramide. Severe extrapyramidal reactions are well recognised in adults. Similar adverse effects have been noted in the paediatric population[367 368].

(b) Domperidone

Domperidone is a peripherally acting dopamine$_2$-receptor antagonist with regulatory effects on the motility of smooth muscle in the gut. It is widely used in adults as an antiemetic and for relief of symptoms of GOR and it appears to have few adverse effects. Only a small number of trials have evaluated the efficacy of domperidone in the newborn. A study of 15 infants aged 3 to13 months reported in 1985 and found that postprandial reflux time improved significantly[369]. They noted minimal adverse effects and concluded that "domperidone is a useful and safe agent" for treatment of GOR in infants. However, it is highly unlikely that a non-randomised study of this size would be sufficient to make conclusive statements on safety of a therapy. Bines *et al* also observed improvement in GOR in patients aged 5 months to 12 years, but only after 4 to 8 weeks of therapy in those with chronic regurgitation and vomiting [370]. There was a large difference in the number of episodes of reflux between the two groups on pH monitoring at the start of the study (69 and 16 episodes for treatment and placebo groups respectively) and study participants were of widely varying ages, making interpretation of results difficult. Carraccio conducted a randomised controlled trial in 80 children between one and 18 months of age[371]. GOR was diagnosed radiologically and on pH monitoring and patients were reported to have "considerably severe" symptoms, but these were not defined further. Randomisation was to one of 4 groups, receiving placebo, domperidone alone, domperidone with alginate or domperidone with magnesium and aluminium hydroxide. They observed no significant improvement in symptoms with either domperidone alone or with alginate compared with placebo. However, they observed improvement with combined domperidone and antacids and concluded that this was a valid therapy for GOR in children. However, without comparison between antacids with and without domperidone, this appears to be an over-interpretation of the data.

Despite this very limited evidence of efficacy in infants, it is likely that domperidone is being used routinely for the management of reflux in both term and preterm neonates, since the use of anti-reflux medications is high in this group[315 329]. The efficacy of domperidone in neonates is still being investigated. Cresi studied 26 infants using combined pH monitoring and MII [372]. Term and preterm neonates were consecutively recruited and randomly assigned

to treatment or control groups. Infants in the treatment group were given domperidone with feeds at 8 and 16 hours after baseline monitoring. All infants were monitored for three consecutive 8-hour periods. Significant increase in the frequency, but decreases in the duration of reflux associated with feeds were observed in the group treated with domperidone, but no difference in the measured pH between groups. The decrease in duration of reflux suggests that domperidone has an effect on gastric emptying, but the increase in frequency is difficult to explain. The authors postulate that these unexpected findings may indicate that the response to prokinetic therapy may be different in the neonate from that in older patients. Hegar *et al* compared domperidone with cisapride in a randomised controlled trial in 20 infants [373]. All infants underwent monitoring of pH and also ECG determination of normal QT interval. Parents of the infants kept daily diaries of symptoms. The number of episodes of regurgitation decreased more during the first week of treatment in the cisapride group, but this difference had disappeared by 2 and 3 weeks of therapy. Differences in pH monitoring were not statistically significantly different between the groups after one month of treatment, although the difference was greater with cisapride than with domperidone and may represent a clinically significant difference. These authors concluded that the two drugs were equally effective for regurgitation, but that cisapride was more effective for GOR. They also stated that "domperidone has a better safety profile".

Of concern then, are recent reports of significant adverse effects with domperidone. Rocha and Barbosa reported the occurrence of QT interval prolongation (as was previously observed with and led to the withdrawal of cisapride) in association with the use of domperidone in an infant[374]. Subsequently, two small studies have been published. Djeddi studied 31 infants with a median gestational age at birth of 33 weeks (range 25-42) receiving oral domperidone for GOR[375]. This study showed a significant difference between gestational ages groups, with prolongation of the QT interval being associated with domperidone administration in infants >32 weeks only, although none developed serious arrhythmia. On the basis of this limited data, the authors suggested that use of the drug might be considered in infants above this gestational age. Günlemez enrolled 43 preterm neonates born between 24 and 33 weeks of gestation treated with domperidone (mean postnatal age 32 days at start of treatment)[376]. All infants had normal electrocardiogram at baseline and two infants developed prolonged QT interval during therapy. This was not statistically significant and both resolved on discontinuation of the drug. However, these finding urge caution in the use of the drug in preterm infants.

(c) Erythromycin

Erythromycin is a macrolide antibiotic that increases gastrointestinal motility by acting as a motilin receptor antagonist[377]. It has been proposed as a useful therapy to improve feed tolerance in neonates. Results of studies have been conflicting and doses used have varied between 1.0 and 12mg/kg 6 hourly; earlier studies generally used higher doses. Ng *et al* showed that oral erythromycin was effective in reducing the time to establish full enteral feeds in VLBW infants randomised to receive the drug (n=27) or placebo (n=29) from 14 days of life after feeds had been commenced during the first 5 days[378]. However, the authors cautioned against the routine use of erythromycin in view of limited data about adverse effects. Costalos and Nuntnarumit confirmed the prokinetic effects of erythromycin at doses of 10-12mg/kg and the earlier establishment of enteral feeding in preterm infants in further randomised controlled trials[379 380]. Oei and Lui investigated the use of low dose (2.5mg/kg) erythromycin from the time of the first feed to promote feed tolerance in 43 infants ≤32 weeks of gestation [381]. Treated infants achieved full enteral feeds earlier than the placebo group; this difference was statistically significant, suggesting that low doses may be effective prophylactically. However, a study comparing low dose erythromycin with placebo for the treatment of feed intolerance in 24 VLBW infants showed that although treated infants reached full feeds earlier, the difference did not reach statistical significance. In contrast to previous studies, El Hennawy *et al* were unable to show any beneficial effect of erythromycin in a further small study involving 26 infants who did not achieve full feeds within 8 days[382]. They were given 1.5mg/kg erythromycin with feeds or placebo for 8 days after pH monitoring and manometry. This study did not find any difference in gastric emptying, gut motility or transit times for feeds, and feeding outcomes were similar between the groups, but the study failed to enrol the intended number of infants based on an a priori sample size calculation. Aly *et al* recently studied 60 infants with feed intolerance randomised to treatment with 1mg/kg erythromycin 8 hourly or placebo[383]. Data from 49 infants were analysed, due to deaths within both groups of similar numbers of infants. Erythromycin use was associated with significantly earlier achievement of full feeds and decreased gastric residual volumes in infants >32 weeks of gestation, but not in less mature infants.

Adverse effects appear to be uncommon with erythromycin, although it has been associated with the development of hypertrophic pyloric stenosis in infants of less than 2 weeks of age[384-386].

Despite the now large numbers of trials that have been conducted in the use of erythromycin, the results remain difficult to interpret because studies have been small and have used widely differing doses of the drug in different populations, in addition to measuring different outcomes. A systematic review of randomised trial concluded that there is insufficient evidence to recommend the use of either high or low dose erythromycin for the management of feed intolerance in preterm neonates.

3.7 Probiotics and prebiotics for the prevention of NEC

Whilst manipulation of feeding strategies and the avoidance of some of the factors thought to be associated with the development of NEC have been proposed as means to reduce the incidence of NEC, few postnatal interventions have been investigated. Intervention that appear most promising to date are the addition of prebiotics or probiotics to enteral feeds. Probiotics are live micro-organisms that can survive in the gastrointestinal tract and confer benefit to the host[387]. Prebiotics are food supplements containing ingredients that selectively stimulate the growth and activity of probiotic bacteria and probiotics are contained in human milk. The mechanism by which NEC is thought to be prevented is colonisation of the gut with beneficial bacteria such as bifidobacteria and lactobacilli, which in turn prevents colonisation by pathogenic strains[388]. There are no randomised trials of prebiotics in preterm infants, but a recent systematic review[389] of probiotic therapy identified eleven trials [390-400]. Meta-analysis suggested clear benefit in terms of reduction of all-cause mortality and prevention of NEC. However, many of these studies were small and a number of different organisms and dosing regimens were used. The authors concluded that evidence was sufficient to warrant a change in practice to include the routine use of probiotics. Others have felt that this response is premature and that further work is needed to determine the optimum probiotic organism or combination of organisms, timing and duration of administration[401 402]. Concerns also exist about the possibility of cross-contamination within the NNU environment, the potential for development of systemic sepsis with these organisms and the long-term effects, which have not yet been examined[403]. In addition, few studies have included the very smallest neonates, for whom the risk of NEC is probably the greatest, and therefore the effects in this extremely important high-risk group are relatively unstudied. Further studies are in progress, which will help to answer such questions, but until these are completed, decisions about the use of probiotics outside the context of clinical trials rests with individual NNUs and clinicians.

3.8 Discussion

A careful review of the research relating to feeding and influences on feeding practice in preterm infants reveals a multitude of gaps in our current knowledge at every level. Much of the published literature has attempted to address the subject of NEC, which accounts for substantial mortality and morbidity in preterm infants and the management of which undoubtedly poses an enormous challenge in the care of this population. Many studies have been designed to clarify facts about disease processes and to inform clinical practice with a view to improving outcomes. Basic science investigation, although active and continually progressing, remains in its infancy and multiple studies have so far been unable to define conclusively a cause for NEC. This is probably due partly to the apparently multifactorial character of the disease, but may also reflect limitations in our current scientific and research methods. It is likely that in coming years our knowledge will increase, but for the present and the foreseeable future, we are faced with a number of potential areas to investigate, some more likely to yield positive results than others, and some of which will almost certainly prove to be "blind alleys".

While basic science progresses, so too does clinical medicine and few specialties are faster growing than neonatology. Clinical researchers strive to understand and interpret results of studies that are available, in an attempt to move ahead and translate these into clinical studies, the results of which might inform clinical practice. Faced with diverse opportunities for research, clinical investigations attempting to determine safe, feasible and effective strategies for managing a seemingly ever less mature newborn population, have been prolific; this in spite of relatively limited robust data on which to base new work. Unfortunately, in clinical studies there have been variations in populations, methodologies and outcome measurements with subsequent conflicting results that have often served only to confuse.

The research "gold standard" of the randomised double-blind placebo-controlled trial is not easily attainable in the preterm neonatal population, due to small numbers of infants and ethical issues surrounding research in the newborn period. Recruitment of adequate numbers of infants needed to detect important outcomes such as NEC with certainty would probably only be achieved through large international trials. Availability of funding for such investigations is limited and amounts required would probably be prohibitive in many cases.

In addition, clinical practice appears to be so variable that the logistic difficulties of determining study protocols that are acceptable to all are considerable. There has recently been a move towards large-scale international trials[285 404] or simultaneous linked trials with planned meta-analysis[405 406], but such endeavours require immense collaborative effort and take many years to complete. Although much needed, there have been no studies of this kind relating to feeding practice in preterm neonates and none are reported to be planned or in development. The current situation is therefore such that evidence from controlled trials comes mainly from multiple small and heterogeneous studies. Meta-analysis has been attempted in many areas to clarify overall findings from such studies, but few conclusions have been drawn.

Partly as a result of challenges in performing randomised controlled trials, large studies of feeding in preterm neonates have, for the most part, been observational in nature. This renders them subject to criticism because of their inability to control many confounding factors and to attribute securely cause-and-effect relationships between risk factors and disease processes. Nevertheless, such studies analysing data from large databases or networks have served as a springboard for much well designed interventional work, albeit often in the form of small studies.

It is not surprising that researchers and clinicians alike are frustrated by the state of the evidence with respect to preterm infant feeding. Many researchers, in published review articles, have come to the reluctant conclusion that, in spite of multiple studies, evidence is insufficient to make recommendations for best practice[407-409]. Others have made impassioned pleas for available evidence to be acknowledged and for the results to be translated into improved clinical practice at the cot side rather than further small studies being conducted[410]; still others have found areas where evidence from good quality studies is completely lacking[330]. For the clinicians delivering care, it is almost impossible to define best practice and it is likely that this will lead to many practising "experience-based" or "opinion-based" medicine rather than supporting evidence-based practice. For those who strive to base their clinical practice on evidence, the dilemma is choosing the most appropriate evidence from studies with conflicting results. The likelihood is that for any given area of practice a wide variety of interpretations of evidence and personal preferences may influence the way in which infant feeding is managed. Potentially, this may lead to either improved or less favourable outcomes. However, if such diversity exists, it is possible that individual clinicians or groups of clinicians within NNUs are not even aware of this.

There are few detailed reports of opinions about feeding of preterm infants and no study has examined the relationship between available research evidence, clinician opinion and clinical practice. The cross-sectional survey reported in this thesis was intended to provide a reference for current practice and to investigate areas where variation in practice may influence neonatal outcomes and in particular NEC. Firstly, it aimed to survey current opinion and reported practice of clinicians caring for premature and very low birth weight newborn infants; secondly, it aimed to document current types of practice, intra- and inter-unit variation with regard to feeding of preterm and very low birth weight infants in selected units in the United Kingdom and Canada. It was necessary to use two different approaches in order to achieve these aims. A semi-structured questionnaire was used to determine opinions of senior neonatologists and paediatricians regularly involved in neonatal care. A retrospective review of medical and nursing records of infants was chosen as the method of obtaining data about current clinical practice. Included infants were those who had been born at a gestational age of less than 30 weeks and / or a birth weight of 1500g or less.

CHAPTER 4

INTRODUCTION TO THE SURVEY

4.1 Perinatal and neonatal care in the UK and Canada

Principles of delivery of health care are similar in both the UK and Canada in that there is a universal health care system, with care being free for all at the point of delivery. However, within neonatal and perinatal care, there are a number of important differences, in part due to the general organisation of service delivery and in part to the huge difference in size between the two countries. Some of these differences in the delivery of care may have the potential to impact upon both pregnancy and neonatal outcomes.

The system for neonatal-perinatal care in Canada is highly regionalised. This system was first proposed in 1970[411] and is now well established. Hospitals within the health care regions are divided into three levels of care: level 1, normal newborn care; level 2, neonatal high dependency care and level 3, neonatal intensive care. In this system, skills and resources necessary to provide advanced neonatal care for the sickest and most premature infants are concentrated within a relatively small number of large centres. Infants are referred to whichever centre has the appropriate level of care to best meet their needs. This centralisation of services means that mothers and babies who require or are likely to require neonatal intensive care sometimes need to travel considerable distances before or after delivery. Repatriation to a lower level unit nearer home will usually be arranged when the baby's condition has improved sufficiently for intensive care facilities to be no longer needed. Since the responsibility for organisation and delivery of care differs between provinces, definitions for levels of care can also be variable and difficult to interpret. The Fetus and Newborn Committee of the Canadian Paediatric Society have recently proposed comprehensive guidelines for a common classification of levels of neonatal care in an attempt to address this difficulty[412].

The concept of restructuring in neonatal care has appeared more recently in England and Wales. Traditionally, a range of care has been provided in most NNUs. Many smaller units generally provide special care, but also have a limited capacity to offer neonatal intensive

care to a small number of babies as necessary. In 2003, a Department of Health working group produced a review of Neonatal Intensive Care Services[413]. Their report proposed the introduction of a system of managed clinical networks with the aim of providing appropriate perinatal and neonatal care as near to home as possible and avoiding the need for mothers and babies to travel unacceptable distances. Four types of unit were defined with corresponding levels of care: midwife-led units providing routine newborn care; level 1, providing routine and special care; level 2, routine, special and high dependency care with some providing short term intensive care if agreed within the network; and level 3 providing routine, special, high dependency and intensive care. The British Association for Perinatal Medicine (BAPM) defines levels of neonatal care in the UK (Table 4.1). Stages of development and organisation of managed clinical networks currently vary across England and Wales and the recommendations do not apply in Scotland. The early period of reorganisation, transition and development that began in 2003 provided the backdrop for this research project within the UK. Transfer of babies from level 3 units to lower level units is common when intensive care is no longer needed. However, many level 3 units have special care facilities to provide ongoing care for babies until discharge from hospital, avoiding the need for transportation.

4.1.1 Staffing of NNUs

Staffing of NNUs and the duties carried out by different members of staff varies between NNUs both within the UK and Canada and between the two countries. Medical training in the UK was reorganised shortly after this study was carried out; this outline of training structure therefore reflects the usual course of training for doctors in paediatrics and neonatology at the time of the study.

Following undergraduate training, medical trainees in the UK completed one year of pre-registration training before deciding the specialty of their choice. They then entered training at the level of Senior House Officer (SHO), lasting for a minimum of 2 years, of which 6 months was spent in neonatal medicine. During this time, professional qualifications in paediatrics would be obtained, allowing entry to the next level of training as a middle grade doctor (Registrar). This comprised 2 years of further training in areas of paediatric medicine, including a minimum of 4-6 months in neonatal medicine. For those wishing to specialise in neonatology, this was followed by a minimum of 3 years of sub-specialty training, of which

24 months was required to be spent in clinical neonatology, allowing opportunities for trainees to pursue interests in research or other areas in the remaining time if desired, although many spent the majority of time in clinical training. Trainees therefore, had undergone a minimum of 5 years postgraduate training in the specialty before taking up a senior position as a Consultant Neonatologist. In addition to training posts in paediatrics and neonatology, some units also employ staff in non-training grades; these are usually at the level of a middle grade doctor.

In Canada, following undergraduate studies, trainees spent 3 years in the junior grade of Paediatric Resident, during which 3-4 months would be spent in neonatal medicine. Following this, doctors wishing to specialise in neonatal medicine entered training as Neonatal Fellows for a minimum of two years. Although this stage of training varied between centres, most spent some time during each year of Fellowship training conducting research, with research time increasing as training progressed. Following completion of sub-specialist training, Canadian trainees are able to take a senior position as an Attending Neonatologist (Staff Neonatologist).

Registered nurses with varying degrees of neonatal training form the mainstay of the nursing workforce. However, in both the UK and Canada, the position of (Advanced) Neonatal Nurse Practitioner (ANNP/NNP) has become a more prominent feature. These nurses undergo additional training of 18 months to 2 years, enabling them to obtain many clinical skills in common with doctors. Only a limited number of NNUs in both countries employ NNPs and their numbers and roles within individual units are very variable. In larger units, however, NNPs often function in a role similar to that of junior doctors and are closely involved in day-to-day medical decision-making.

In Canada, in addition to medical and nursing personnel, other groups of professionals are often employed in NNUs. Respiratory therapists (RTs), who are specifically trained in all aspects of respiratory management of neonates, undertake much of the day-to-day ventilatory management of infants. Also linked to units are neonatal dietician-nutritionists, who are closely involved with the nutritional management of babies. Although common in Canadian units, RTs do not exist in the UK and only a very small number of NNUs have access to a specialist in neonatal dietetics.

During this study period, therefore, large numbers of individuals with varying degrees of experience and expertise are likely to have been involved in the care of babies in the units surveyed. Whilst it is impossible to determine different levels of staffing and skill mix associated with care of babies in this study, it is important to recognise that this is one of many factors that may influence decision-making with respect to feeding.

Table 4.1: Levels of care defined by BAPM

Normal routine care	Care of babies well enough to be at home but remain in hospital because the mother needs support. This may include care of mothers of mature preterm infants or babies with minor or common medical problems
Special care	Continuing care for babies who require specialist support such as tube feeding or care in incubators, for example well babies who are maturing after preterm delivery or convalescing following high dependency or intensive care
High dependency care	Specialist cares for babies who, though not critically ill require continuous support and observation for neonatal conditions. Examples are preterm babies with recurrent apnoea spells, stable babies receiving nasal CPAP or those receiving PN
Intensive care	Critically ill babies who require continuous support for organ failure and continuous observation, examples being babies who require ventilation or very preterm babies with respiratory distress syndrome

4.2 Ethics and consent

4.2.1 Research ethics approval

Research ethics approval for this work was sought from the Multicentre Research Ethics Committee (MREC) in the UK. The research was approved in August 2004. Since the survey was to be carried out by a single researcher, this approval was granted under supplementary regulations. These regulations stated that where no local researcher is appointed, it was a requirement only to inform relevant local research ethics committees, rather than to gain

formal ethical approval for each centre involved. Copies of the survey protocol, study documentation and MREC approval letters were therefore sent to each local committee for information.

The survey protocol and documentation were submitted for consideration by the Research Ethics Board of Hamilton Health Sciences / McMaster University in Canada in July 2005. Approval was granted in August 2005. In Canada, there is no established system for ethical approval of work involving collection of patient data to be undertaken on multiple sites. It was therefore necessary to submit further individual and full applications to the Research Ethics Boards for each centre to be involved. The regulations for ethical approval in Canada stated that the Principal Investigator for any research study must be a registered Canadian practitioner in a substantive post at the institution where the research was conducted. This necessitated identification of and liaison with a staff neonatologist in each unit who was willing to take responsibility for the survey in this capacity. Applications for ethical approval were submitted to five hospitals in Ontario and Nova Scotia. However, due to limitations caused by the time constraint of one year for the research in Canada, long distances between centres and the duration of the application process, approval was obtained for only three centres in Ontario.

4.2.2 Ethical Issues in clinical practice

The development of neonatology as a subspecialty of paediatrics has taken place in the relatively recent past. Although research in the area is progressing and the body of knowledge is growing rapidly, there remains a paucity of published evidence from well-designed and conducted research in many areas. In such aspects of practice, those involved in neonatal care must rely heavily on data from small studies or trials, supplemented by knowledge from unit or personal clinical experience. The use of clinical guidelines and frameworks for practice is becoming more widespread in NNUs, but is not yet universal. Examination of the resulting variation in clinical practice can be considered to be a sensitive issue, since there may be a risk of clinicians feeling vulnerable to criticism and comparison of their personal practice with that of others. The information sheet circulated with the questionnaire therefore contained a statement assuring clinicians that centres and participants would be identified only by unique identification codes and that no specific comparisons would be made between identified individual NNUs or practitioners. Although no explicit

written consent to take part in the survey was obtained, completion and returning of the questionnaire were regarded as implied consent. The voluntary nature of participation was highlighted. The information sheet was designed in accordance with guidance offered by the Central Office for Research Ethics Committees (COREC) in the UK.

4.2.3 Consent for research in neonates

For interventional research in the newborn, it is essential to obtain explicit written informed consent from parents before an infant can be included. The issues surrounding collection of anonymised infant data are less clear. For retrospective data collection, research requiring parental consent is limited by the ability of the researcher to locate and contact parents for discussion of the research aims and requirements. This problem is magnified in work that involves large numbers of infants who are no longer hospitalised and the inclusion of multiple centres over wide geographical areas. The subject of parental consent for this survey was carefully considered and was discussed with senior neonatologists and members of ethical committees at an early stage in the planning of both the pilot and definitive surveys. A requirement for fully informed consent from all parents of babies, both surviving and those who had died, would almost certainly have rendered this survey impractical. It would also have been likely to compromise the integrity of the work by introducing selection bias. Since epidemiological research of this kind relies heavily on the completeness of data, the approving research ethics bodies agreed that written parental consent was not required. The approach was taken whereby all data were anonymised and no patient identifiable data were removed from the hospital premises at any time.

PART II

CLINICIAN SURVEY OF FEEDING PRACTICE

CHAPTER 5

SURVEY DESIGN

A semi-structured questionnaire was designed as a tool to examine the opinions and reported practice of clinicians with respect to the initiation, progression and temporary discontinuation of milk feeds in preterm and very low birth weight infants. It aimed to determine the availability of written clinical practice guidelines on the subject of infant feeding and clinicians' preferences for feeding strategies. Specifically, it included questions to identify those factors that influence clinicians in their decisions about feeding preterm and very low birth weight infants.

5.1 Piloting and peer review

There has been no recent work designed to address these questions and no previously validated questionnaires or datasets suitable for modification. The questionnaire was therefore constructed specifically for this research. A study piloting the use of a questionnaire was carried out in Scotland in 2003[1]. This provided the opportunity to test the methodology on a subset of the intended final population and to assess the feasibility of performing a more extensive survey. Prior to the piloting of the clinician survey, the questionnaire was administered informally to a small number of neonatologists who would not be involved in the survey. They provided comments and feedback on the layout, length, language, content, clarity and acceptability of the questionnaire and identified any ambiguities or omissions. This peer-review process led to only minor changes in the wording of the questionnaire. At this stage, questions on all potentially significant factors that might be expected to affect either feeding practice or feeding-related outcomes were included. This allowed identification of the most and least relevant factors and subsequent refinement of the survey for more widespread use. For the pilot survey, face-to-face interview was chosen as the most feasible method of administration and the method most likely to obtain the maximum number of responses. This approach also provided clinicians with the opportunity, during interview, to provide feedback on the content and administration of the survey. A single researcher interviewed one consultant neonatologist in each of fifteen Scottish NNUs.

Suggestions that were consistently made by respondents were then used to make amendments when producing the subsequent version used for the current survey.

5.2 Questionnaire content

The content of the clinician questionnaire was modified firstly on the basis of experience with using the questionnaire during piloting and secondly as a result of feedback from clinicians taking part in the pilot survey.

Following analysis of the results of the pilot survey, it appeared that the list of factors chosen as those that might significantly influence feeding practice was appropriate. Most of the factors presented were considered to be a potential influence on decision-making by more than 25% of clinicians. During the pilot survey, neonatologists had been given the opportunity to identify any other areas they felt had been omitted. Many of them identified one or more additional factors that might influence their practice. However, no more than one clinician highlighted any single factor. It was therefore thought that the addition of a number of other factors to the list might not yield a substantial number of additional responses and that a lengthier list might serve to discourage participation. However, several clinicians had felt that signs and symptoms of NEC should be included in the list. This had previously been thought unnecessary, since it had been anticipated that there would be consistent and unanimous agreement among neonatologists about discontinuation of feeds in babies displaying symptoms of NEC. However, in view of this feedback, four further factors were added: mild abdominal distension, severe abdominal distension, bloody stools and abdominal tenderness. One other factor – blood transfusion – was also added since the appropriateness of feeding infants during transfusion had been highlighted recently as a topic of interest in professional internet discussion forum, "NICUnet". Three factors that had been included in the pilot survey were removed. 'Lack of MEBM' and 'lack of any breast milk' were considered inappropriate as answers to these questions might more closely reflect the inconsistent availability of donor bank expressed milk rather than true clinician preference. The third factor to be omitted in the definitive survey was 'patent ductus arteriosus'. This was felt to be less discriminating than questioning about the administration of indomethacin for treatment, since this was the more usual reason cited by clinicians for slowing or discontinuing milk feeds in infants with patent ductus arteriosus.

5.3 Survey participants

During training in paediatric and neonatal medicine, junior doctors frequently work in a number of different departments and are therefore exposed to many different opinions and practices for all aspects of care, including the feeding of infants. This exposure allows development and shaping of an individual's own clinical practice. It is expected that by the time of attaining a substantive position as a consultant or attending paediatrician or neonatologist, a clinician will have had sufficient experience to have developed their views to the extent where they would be able to give an informed opinion regarding aspects of neonatal care. It was decided, therefore, that clinicians to be invited to take part in this survey should be senior enough to have formulated individual opinions and be likely to have been employed in the same NNU for a significant period of time. In the UK, all consultant neonatologists and paediatricians regularly involved in the care of newborn infants were approached. In Canada, all staff neonatologists working in Level 3 neonatal intensive care units were included.

5.4 Layout and structure of the questionnaire

The questionnaire was first designed for use in the UK and consisted of five short sections, labelled A to E for ease of reading. Section A included general questions to obtain background information about the size of the NNU and type of care offered, including availability of PN and DEBM. The subjects of initiation, progression and temporary discontinuation of feeds were addressed in the following three sections (B, C and D respectively) in the logical order in which these decisions would usually be taken in the clinical situation. The layout of questions in each of these sections followed a similar pattern. In each of the three sections, clinicians were asked about the availability firstly of general and secondly, more specific written guidelines for feeding of preterm and low birth weight babies on their NNU. It would be expected that centres with comprehensive feeding guidelines would show less variation in practice, since personal opinion would be likely to play less of a part in decision-making. For the initiation of feeds, the clinicians' views on the optimum time for introduction of milk was sought, as well as opinion on the most suitable type and volume of milk for this. Section C addressed the rate of progression to full enteral feeds. Section D, addressed the temporary discontinuation of feeds and clarified criteria used for this and personnel involved most often in the decision-making process.

Section E addressed all specific single clinical factors previously identified as those potentially associated with important or adverse outcomes related to preterm infant feeding. Clinicians were asked to consider each factor with respect to initiation, progression and discontinuation of feeds and to decide whether or not the presence of each factor influenced decision-making on the NNU. Items on the list were clearly numbered from 1 to 30, with the final section allowing clinicians to identify any factors they considered important, but not included in the list.

Closed, structured questioning requiring Yes / No answers was used as far as possible to facilitate comparison and quantitative analysis of the responses. Where this was not possible because the range of responses was difficult to predict or likely to vary from one clinician to another, doctors were asked to respond using their own words. Adequate free text space was provided for this. It was hoped that this section might elicit some responses including factors that would be repeated later in the questionnaire in the form of closed questions. The purpose of this was to act as a measure of internal consistency. Similarly, some of the factors included in Section E, such as "hypotension" and "use of inotropes" were closely related, as are "vomiting" and "large aspirates". Similar responses to these questions would be anticipated, since they are essentially measures of the same things and would also confirm internal consistency.

The topic-based layout and wording of the questionnaire was intended to be as succinct and simple as possible, whilst acknowledging that both the researcher and all respondents are trained in the same discipline and are familiar with terminology and procedures in neonatal medicine.

5.4.1 Adaptation of the questionnaire for use in North America

The layout and structure of the questionnaire used for Canadian neonatologists was identical to that of the UK document. However, a number of minor revisions were necessary to adapt the questionnaire for use in Canada to reflect transatlantic differences in terminology and spelling. The main difference was in the terminology referring to neonatal staff personnel, which differs between the countries.

CHAPTER 6

SURVEY PROCESS

6.1 Identification of potential participants

6.1.1 United Kingdom

Contact details of consultant neonatologists in the UK were obtained from the Handbook of the British Association of Perinatal Medicine (BAPM) after first informing the BAPM that the survey was about to be circulated. Since many consultant paediatricians are not members of the BAPM, but have significant input into neonatal care, further information was obtained from the 2003 Handbook of the Neonatal Nurses Association, which lists neonatal and special care baby units and provides names of clinicians associated with these units. Special interests of consultants were checked using the Internet website www.specialistinfo.com. Consultants who identified "neonatology", "neonates", "neonatal medicine" or "perinatal medicine" as a special interest in their professional details were included in the distribution list. Both publications that were used to compile the distribution list are freely available to practising clinicians within neonatology. The website is accessible after registration and independent verification of professional details. Although it was acknowledged that these methods would be likely to identify some paediatricians who no longer work with the newborn following reorganisation of services and workloads, it was felt to be important to avoid exclusion of any who were potentially involved in neonatal care.

6.1.2 Canada

The Canadian Neonatal Network™ is a group of Canadian researchers who collaborate on research issues relating to neonatal care. The Network was able to provide contact details of NNU Medical Directors. Canadian NNUs have substantially more input from dedicated neonatal dietician-nutritionists than is customary in UK units. It is usual for them, as well as neonatologists, to make ongoing decisions and suggestions about feeding of high-risk

infants. Similarly, neonatal dietician-nutritionists are significantly involved in the development and implementation of feeding guidelines. Given this fundamental difference, it was decided that questionnaires should be distributed to one neonatal dietician from each NNU included in the survey. Members of the Neonatal Dieticians' Group in Canada were able to provide a distribution list to facilitate contact with dietician-nutritionists.

6.2 Administration of the questionnaire

Clinicians interviewed during the piloting stage of the survey expressed the view that the questionnaire might be appropriately administered by post or email in future surveys. Given the much greater numbers of clinicians involved in the present work, this approach was adopted. The questionnaire, together with a letter and information sheet about the aims of the survey, was distributed by post to identified consultant neonatologists and paediatricians in the UK. Stamped addressed envelopes were included for responses.

In Canada, NNU Medical Directors were approached by email via the Canadian Neonatal Network, informing them of the survey and requesting permission to send the questionnaire to neonatologists within the unit. The questionnaire and information sheet were then distributed by email to clinicians, inviting responses by either email or post.

6.2.1 Non-responders

Following distribution of questionnaires by post to UK clinicians, a follow-up email was sent to all those from whom a response had not been received within one month, together with a request for any clinicians who felt that they had been inappropriately included in the mailing to confirm this, giving their reasons. Similarly, a follow-up email was sent to Canadian clinicians.

CHAPTER 7

SURVEY RESULTS

In total, 854 questionnaires were distributed by post to clinicians in the UK between September and December 2004 and to clinicians in Canada between May and September 2005. Of these, 740 (86.7%) recipients were neonatologists or paediatricians working in 175 UK NNUs. Ninety-eight (11.5%) were neonatologists and 16 (1.9%) were dieticians in 23 Canadian NNUs.

7.1 Participant inclusion

7.1.1 United Kingdom

Of the 740 UK clinicians who received questionnaires, 60 replied in writing, but indicated that they believed they had been inappropriately included in the survey. Reasons given were: retired (n=2), no longer in post (n=10) and no longer responsible for the care of preterm and low birth weight newborn infants (n=48).

In an attempt to identify others who had not replied but may have been inappropriately contacted, each NNU was telephoned to ensure that (i) the unit was still caring for infants within the relevant gestational age and weight groups and (ii) each clinician still maintained active participation in neonatal care. As a result of this, 7 NNUs (18 clinicians) were identified as either having closed or discontinued care of infants <30 weeks of gestation. A further 30 individual clinicians were identified as no longer being involved in the care of infants ≤30 weeks' gestation and 7 clinicians had moved to other positions.

Therefore, in order to ensure that the dataset contained details only of clinicians who take a significant part in neonatal care, 115 clinicians, to whom questionnaires had originally been sent, were therefore excluded from the denominator data. Numbers of clinicians and reasons for exclusion are shown in Table 7.1. This reduced the total number of clinicians that were in the intended UK target population for questionnaire administration to 625. This figure was

therefore used as the denominator when analysing UK questionnaire responses. These clinicians worked in 168 NNUs.

Table 7.1: Reasons for exclusion of UK clinicians

Reason for exclusion	Number of clinicians
No longer involved in neonatal care	96
Retired from clinical practice	2
Moved to another place of work	17
Total number of clinicians excluded	**115**

7.1.2 Canada

There were 114 questionnaires sent to clinicians working in Canadian NNUs. Contact details for Canadian clinicians were obtained directly from the chief neonatologists of the units, so it was therefore possible to confirm the status of doctors and dietician-nutritionists at this time. All clinicians to whom questionnaires were distributed were employed in NNUs that cared for infants within the relevant gestational and birth weight groups at the time of the survey.

7.1.3 "Unit-based" responses

Several clinicians (19 neonatologists from 12 UK NNUs and 1 Canadian neonatologist) requested to be considered in the analysis as part of a "unit response" rather than each clinician within a unit being required to complete an individual questionnaire. Reasons given for this on were (i) that unit guidelines for feeding were in place to which all clinicians adhered and (ii) that the lead neonatologist would be most appropriately informed to be able to give an opinion reflecting that of the whole clinician group.

Clinicians who suggested that they would prefer to submit a unit-based response were contacted to re-emphasize the study aim of documenting intra-unit variability in opinion and practice. However, all stated that they believed that feeding practice did not differ between clinicians and that guidelines, where present, were closely followed. All declined to

complete an individual questionnaire and said that one view would be likely to reflect those of all clinicians.

Had the suggested approach been used, the opinions and reported practice of 55 clinicians would have been reflected in responses from only 12 clinicians. This would be acceptable if there was certainty that the views of all clinicians within a given unit would be identical; however, it was felt that this would be unlikely. In order to test this, all completed questionnaires from NNUs where one or more clinicians had requested that a unit-based response should be accepted were examined. Completed questionnaires had been received from more than one clinician (range 2-5) in four of the 12 NNUs. Detailed examination of these questionnaires revealed that the responses were not identical in any case and were substantially different in some. Table 7.2 shows the number of clinicians in these NNUs and the number of questionnaires that were returned, together with the percentage of questions that were answered in the same way by all responding clinicians. For one of the NNUs where at least one clinician expressed the view that a unit response would be preferable, no completed questionnaire was received. In view of this, only completed and returned questionnaires from these units were included; all other clinicians were regarded as non-responders.

Table 7.2: Agreement between questionnaire responses in units requesting inclusion of unit-based responses

Total number of clinicians in unit	Number of completed questionnaires	Agreement between questionnaire responses
6	5	43.4%
7	4	64.6%
6	3	54.5%
4	2	77.7%
3	1	
3	1	
8	1	
5	1	
4	1	
3	1	
3	1	
3	0	

7.2 Response rates and respondents

There were 277/625 responses (44.3%) from clinicians in the UK and 45/114 from Canada (39.4%). Requests from 20 clinicians who did not complete the questionnaire, but wished to be included based on a response from someone representing the whole unit, were excluded. After exclusion of these clinicians, the total number of valid responses was 302 (40.9%) with 258 (85.4%) from UK clinicians and 44 (14.6%) from Canadian clinicians. The response rate from UK clinicians was slightly higher than from Canadian neonatologists or dietician-nutritionists and these are summarised in Table 7.3.

152 of the 191 NNUs involved in the survey returned at least one completed questionnaire (79.6%). 135/168 (80%) UK units and 17/23 (74%) Canadian units returned at least one questionnaire.

Table 7.3: Response rates by clinician groups

	Number of clinicians	Completed questionnaires	Response rate
UK neonatologists/ paediatricians	625	258	41.3%
Canadian neonatologists	98	39	39.8%
Canadian neonatal dieticians	16	5	31.2%
Total	**739**	**302**	**40.7%**

7.2.2 Characteristics of UK respondents

Of the 625 UK clinicians included in the survey, 354 (56.6%) were identified, on the internet website 'www.specialistinfo.com' either as neonatologists or as paediatricians with a special interest in neonatology. 203 (57.3%) of these clinicians completed and returned questionnaires, accounting for 78.4% of all valid responses. This indicated that those specialising in neonatal medicine were significantly more likely to respond (χ^2 test, P=0.006) to this survey than were general paediatricians who had some, but not full time, commitment to the neonatal service.

7.2.3 Characteristics of Canadian respondents

In contrast to the UK system, in Canada there is little day-to-day "cross cover" between paediatric and neonatal services by clinicians in NNUs that care for very low birth weight infants on a regular basis. Only such units were contacted, therefore this negated the need to clarify whether clinicians were spending all their time in neonatal care, as this is the norm and all are regarded as specialists in neonatal medicine.

7.3 Availability of Parenteral Nutrition

Three hundred (99%) clinicians said that PN was available in their NNU. All Canadian units had PN. Two respondents from two different UK units stated that it was not available. However, one of these responses conflicted with the response of another clinician from the same NNU that indicated the availability of PN.

7.4 Availability of Donor Expressed Breast milk

7.4.1 United Kingdom

All but one UK clinicians answered this question. Ninety-four (31%) clinicians, in total, stated that donor expressed breast milk (DEBM) was available on their NNU. DEBM was more widely available in the UK. There were positive responses from at least one clinician in 54/135 (40%) units. However, there were conflicting responses from 10/135 (7%) units, suggesting that the true percentage of units having access to DEBM is probably somewhere between 32% and 40%.

7.4.2 Canada

Only two neonatologists and one dietician, each from different NNUs in Canada said that they had access to DEBM (7%). The dietician stated that it had become available to the NNU only very recently; however, all responses from neonatologists in that unit indicated that it was not available to them. With respect to the two other positive responses, one was from a unit from which this was the only response; the other was in conflict with the

responses of colleagues from the same NNU. These results suggest that DEBM was only available in between 1 and 3 (6-18%) of the 17 Canadian units responding.

7.5 Use of Feeding Guidelines

Clinicians were asked to state whether their NNU had written guidelines for each of three areas of feeding practice: (1) initiation of enteral feeds, (2) rate of advancement of enteral feeds and (3) criteria for the temporary discontinuation of enteral feeds. They were also asked (4) whether the unit routinely used a defined minimal enteral feeding regimen.

7.5.1 Initiation of enteral feeds

7.5.1.1 United Kingdom

256 UK clinicians answered the question about guidelines for the initiation of feeds. There was at least one response from 134 NNUs. Of these, 58 NNUs were represented by a response from a single clinician. From the remaining 76 units, at least two responses were received (range 2-7). 134 (52%) clinicians answered that written guidelines were available on their NNUs and 122 (48%) answered that guidelines were not available.

7.5.1.2 Canada

Forty-four clinicians from the 17 Canadian NNUs answered this question. Of these, 12 NNUs were represented by a response from a single clinician. From the remaining 5 units, at least two responses were received (range 2-7). Thirty-six (82%) clinicians answered that written guidelines were available on their NNUs and 8 (18%) answered that guidelines were not available.

7.5.2 Advancement of enteral feeds

7.5.2.1 United Kingdom

Two hundred and fifty-five UK clinicians submitted a response about guidelines for the rate of advancement of feeds. There was at least one response from 134 NNUs. Of these, 59 NNUs were represented by a response from a single clinician. From the remaining 75 units,

at least two responses were received (range 2-7). One hundred and two (40%) clinicians answered that written guidelines were available on their NNUs and 153 (60%) answered that guidelines were not available.

7.5.2.2 Canada

Forty-three Canadian clinicians answered this question, with at least one response received from each of the 17 NNUs. Of these, seven NNUs were represented by a response from a single clinician. From each of the remaining 10 NNUs, at least two responses were received (range 2-7). Thirty-nine (91%) clinicians answered that written guidelines were available on their NNUs and 4 (9%) answered that guidelines were not available.

7.5.3 Temporary discontinuation of enteral feeds

7.5.3.1 United Kingdom

There were 252 responses from UK clinicians about temporary discontinuation of feeds. There was at least one response from 133 NNUs. Of these, 59 NNUs were represented by a response from a single clinician. From each of the remaining 74 units, at least two responses were received (range 2-7). Only 42 (17%) clinicians answered that written guidelines were available on their NNUs and 210 (83%) answered that guidelines were not available.

7.5.3.2 Canada

Forty-three clinicians from the 17 Canadian NNUs answered this question. Of these, 7 NNUs were represented by a response from a single clinician. From the remaining 10 units, at least two responses were received (range 2-7). Twelve (30%) clinicians answered that written guidelines were available on their NNUs and 31 (70%) answered that guidelines were not available. Table 7.4 summarises the total number of positive responses received from individual clinicians and the number of NNUs that were represented.

7.5.4 Minimal Enteral Nutrition

7.5.4.1 United Kingdom

There were 254 responses from UK clinicians in 134 NNUs. There was at least one response from all NNUs. Of these, 61 NNUs were represented by a response from a single clinician.

From each of the remaining 73 units, at least two responses were received (range 2-7). 123 (48%) clinicians answered that their NNU used a defined minimal enteral feeding regimen and 131 (51%) answered that it did not.

7.5.4.2 Canada

All clinicians returned a response to this question. Seven of the 17 NNUs were represented by a single clinician's response. Between 2 and 7 responses were received from the other 10 units. Twenty-eight (64%) clinicians indicated that their NNU routinely used a minimal enteral feeding regimen and 16 (36%) indicated that they did not.

Table 7.4: Positive (Yes) responses indicating the availability of written feeding guidelines on NNUs

	UK No. (%) clinicians	Canada No. (%) clinicians	Total No. (%) clinicians
1. Does your NNU have written guidelines on the initiation of enteral feeds?	134/256 (52%)	36/44 (82%)	178/300 (59%)
2. Does your NNU have written guidelines on the rate of increase of enteral feeds?	102/252 (40%)	39/43 (91%)	141/295 (48%)
3. Does your NNU have written criteria for the temporary discontinuation of enteral feeds?	42/252 (17%)	12/43 (30%)	54/295 (18%)
4. Does your NNU routinely use a defined minimal enteral feeding regimen?	123/254 (48%)	28/44 (64%)	151/298 (51%)

7.5.5 Intra-unit variation in responses

For Questions (1), (2), (3) and (4) there was more than one response from 86, 85, 84 and 83 NNUs respectively. There was substantial variation in responses between members of teams within individual NNUs in the UK and in Canada. In NNUs from which more than one response was received, these were conflicting >25% of the time for all questions and approaching 50% of the time for the final question. Results are summarised in Table 7.5.

Where only one response was returned from a single clinician, based on the available data, it could only be assumed that these responses correctly reflected the status of the NNUs at the

time of the survey. For all units from which conflicting responses were received it is uncertain as to whether guidelines were, or were not available at the time of the survey.
The survey results therefore suggest the following:

1. Guidelines for feed initiation may be available in between 42% and 64% of UK NNUs and in between 59% and 88% of Canadian units.
2. Guidelines for the rate of advancement of feeds may be available in between 31% and 48% of UK units and in between 70% and 82% of Canadian units.
3. Guidelines for discontinuation of feeds may be available in between 10% and 23% of UK NNUs and in between 12% and 47% of Canadian units.
4. A defined minimal enteral feeding regimen is used routinely in between 39% and 63% of UK NNUs and in between 41% and 76% of Canadian units.

Table 7.5: Results for NNUs from which two or more responses were received

	UK Responses			Canada Responses			Total conflicting responses
	Yes	No	Conflicting	Yes	No	Conflicting	
1. Does your NNU have written guidelines on the initiation of enteral feeds?	25	22	29 (38%)	5	0	5 (50%)	34/86 (39%)
2. Does your NNU have written guidelines on the rate of increase of enteral feeds?	17	36	22 (29%)	7	1	2 (20%)	24/85 (28%)
3. Does your NNU have written criteria for the temporary discontinuation of enteral feeds?	3	54	17 (23%)	1	3	6 (60%)	23/84 (27%)
4. Does your unit routinely use a defined minimal enteral feeding regimen?	20	20	33 (45%)	3	1	6 (60%)	39/83 (47%)

7.5.6 Specific Guidelines

In addition to questions about the three main areas of feeding practice, clinicians were asked whether their NNUs had any specific guidelines for the initiation or advancement of feeds in any particular subgroups of babies. One hundred and nine clinicians stated that they had

guidelines for initiation of feeds for one or more different subgroups of babies and 72 that they had such guidelines for feed advancement. The types of babies were similar for both aspects of feeding and the numbers of responses are summarised in Table 7.6. The most common conditions for which guidelines had been developed were growth restricted babies and those with abnormal umbilical antenatal doppler studies. Several clinicians indicated that specific guidelines were available based on birth weight < 1500g, <1250g or <1000g, or based on gestational age <24 weeks, <28 weeks, <30 weeks or <32 weeks. Others suggested that guidelines were different according to "high risk" or "risk of NEC", although these risks were not defined. Most clinicians did not specify only one group of infants, but indicated that a number of different specific guidelines were available in their units.

Table 7.6 Groups of babies for whom specific guidelines were available

	Feed initiation (No. clinicians)	**Feed advancement (No. clinicians)**
Abnormal dopplers	51	24
IUGR	37	23
Based on birth weight	39	9
Based on gestational age	10	4
Birth asphyxia	8	3
High risk or risk of NEC	8	9
Risk of hypoglycaemia	7	1
Inotropic support	2	0
Surgical conditions	5	7
Polycythaemia	3	1
Umbilical catheters	1	0
Pharmacological paralysis	2	0
Delayed passage of meconium	1	1
Indomethacin	1	0
Sick	4	4
Based on SMA flow	1	1

7.6 Introduction of enteral feeds

Clinicians were asked what they considered the optimal time for introducing breast milk feeds where this is available and there is no specific contraindication to introducing enteral feeds. 258 UK and 41 Canadian clinicians answered this question. The majority favoured the early introduction of enteral feeds with more than 90% preferring to introduce milk within 48 hours of birth. Twenty (6.6%) considered that feeds should be started between day 3 and day 7 of life. No clinician would delay the introduction of breast milk for a week or more in the absence of specific contraindications (Table 7.7).

Table 7.7: Perceived optimal time for introducing enteral feeds

	UK Responses (n=258)	Canada Responses (n=44)	Total Responses
Day 1	150 (58%)	25 (57%)	175 (58%)
Day 2	88 (34%)	14 (32%)	102 (34%)
Day 3-4	17 (6%)	2 (4%)	19 (6%)
Day 5-7	1 (<1%)	0	1 (<1%)
> 7 days	0	0	0
No response	2 (<1%)	3 (7%)	5 (2%)

7.6.1 Delayed introduction of feeds, awaiting maternal breast milk

Clinicians were asked how long they felt it would be acceptable to delay the start of feeds while awaiting MEBM. Responses were very variable and are summarised in Table 7.8; there were three non-responders (1%), all from the UK. 15 (5%) clinicians from units where donor breast milk was available would use this to introduce feeds when indicated.

Table 7.8: Delay in introducing enteral feeds while awaiting maternal milk

Acceptable delay	UK Responses (n=258)	Canada Responses (n=44)	Total Responses
≤24 hours	53 (20%)	19 (43%)	72 (24%)
≤ 48 hours	84 (33%)	10 (23%)	94 (31%)
≤ 3 days	40 (15%)	11 (25%)	51 (17%)
≤ 4 days	13 (5%)	2 (4%)	15 (5%)
≤ 5 days	12 (5%)	0	12(4%)
≤ 6 days	1 (<1%)	0	1 (<1%)
≤ 7 days	6 (2%)	1 (2%)	7 (2%)
Would use donor milk	15 (6%)	0	15 (5%)
Would always await MEBM	9 (3%)	0	9 (3%)
Guided by parents' wishes	3(1%)	0	3 (<1%)
Variable periods, not specified	19 (7%)	1 (2%)	20 (7%)
No response	3 (1%)	0	3 (<1%)

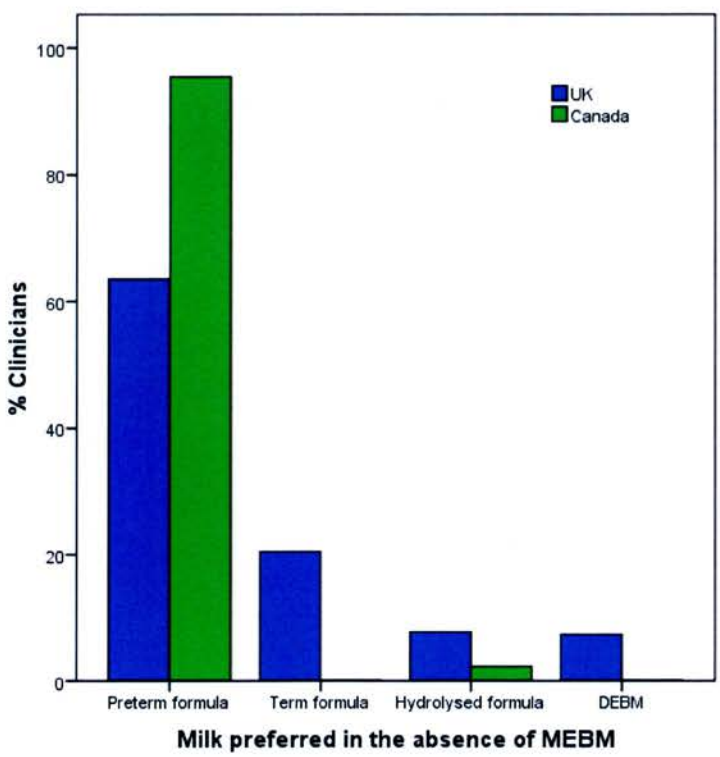
7.6.2 Type of milk

It is accepted that when maternal breast milk is available, this is the milk of choice for the introduction of feeds in preterm infants. In the absence of MEBM, a number of choices are available to the clinician. Clinicians were therefore questioned about their choice of milk to use for preterm infants in circumstances where a mother is unable or does not wish to express milk, or for whom breast-feeding is contraindicated. Responses for this question are summarised in Figure 7.1. 19 (7%) clinicians from 12 NNUs said that donor breast milk would always be available on their NNUs and that this would be their preferred choice in the absence of maternal milk. A further 11 indicated that their choice would be different, depending on whether the baby was considered "high risk or "low risk". These responses indicated that high risk was based on criteria including birth weight < 1000g or <1200g, gestation <26 weeks, severity of illness or abnormal Doppler flow measured antenatally in umbilical vessels. Of the clinicians who would usually use preterm formula, 11 would consider the use of donor milk in high-risk babies, one would use term formula and five would use a hydrolysed protein formula. Of those choosing a term formula for routine use, four would give hydrolysed formula to high-risk babies.

7.6.2.1 Intra-unit variation

There was more than one response to this question from 75/134 (56%) NNUs. Of these, 53 (71%) responses were in agreement about the preferred milk. From the remaining 16 units (22 UK; 1 Canadian), there were two (n=22) or 3 (n=1) different responses. The most common difference in opinion was a choice between preterm or term formula, which occurred in 11 units. Preterm or hydrolysed formulas were the choices in four units (3 UK; 1 Canadian). In other units where there were differences (n=8), opinions were variable, with preterm, term or hydrolysed formula each being chosen by one clinician, and donor breast milk by another.

Figure 7.1: Choice of milk in the absence of maternal expressed breast milk



7.6.2.2 Initial feed volumes and frequency

Clinicians were asked to state the usual starting volume and frequency for enteral feeds given to infants of ≤1500g birth weight and/or gestational age of <30 weeks in their NNUs. 294 (97.3%) clinicians provided responses to one or both parts of this question. Eight chose not to answer and one provided information about volume, but not frequency of feeding. Ten clinicians stated that their practice for both feed volumes and frequency was variable, but did

not give reasons for this. A further 16 clinicians clarified that their practice varied depending on the birth weight or gestation of the baby. There was, in addition, considerable variation in responses, both in terms of actual volumes and frequencies reported and the way in which they were quantified. Starting volumes were variably expressed in ml/feed, ml/hour, ml/kg/feed or ml/kg/day. Frequently a range of volumes and frequencies was suggested. Single feed volumes ranged from 0.1ml to 2ml and frequency of feeding ranged from every 12 hours to every hour. Hourly feeds were most commonly used, with 114 respondents using this regimen. The range of responses is summarised in Tables 7.9 and 7.10. Table 7.10 also shows the variation in feed volumes that would be administered in a 24-hour period and the implication that this would have for the amount of enteral feed given to a preterm baby with a birth weight of 750g, were these volumes and frequencies applied.

Table 7.9: Feed volumes and frequency

Feed volume	No. clinicians
0.1 – 0.5 ml/feed	4
0.5 ml/feed	54
0.5 – 1 ml/feed	38
1 ml/feed	79
1 – 2 ml/feed	7
2 ml/feed	2
0.5 – 1 ml/kg/feed	6
1 ml/kg/feed	29
3 – 10 ml/kg/day	3
10 ml/kg/day	4
10 – 20 ml/kg/day	12
20 ml/kg/day	9
12 – 24 ml/kg/day	1
20 – 40 ml/kg/day	2
30 ml/kg/day	1
60 ml/kg/day	18
60 – 90 ml/kg/day	2
Dependent on gestational age	4
Dependent on birth weight	8

Feed frequency	No. clinicians
Hourly	114
1 – 2 hourly	10
1 – 3 hourly	2
1 – 4 hourly	6
2 hourly	30
2 – 3 hourly	4
2 – 4 hourly	4
2 – 6 hourly	1
3 hourly	10
3 – 4 hourly	4
4 hourly	27
4 – 6 hourly	5
6 hourly	13
2 – 12 hourly	2
6 – 12 hourly	4
12 hourly	4
Continuous	7

Table 7.10: Feed volumes and intervals; range of responses

Feed volume	Feed interval	Expected feed vol. /24 hours	Expected feed vol. /24 hours (750g infant)
0.1-0.5 ml/feed	4 hourly	2.4 – 12 ml	2.4 – 12 ml
0.5 ml/feed	1 – 12 hourly	1 – 12 ml	1 – 12 ml
0.5-1 ml/feed	1 – 12 hourly	1 – 24 ml	1 – 24 ml
1 ml/feed	1 – 12 hourly	2 – 24 ml	24 ml
1-2 ml/feed	2 – 12 hourly	2 – 24 ml	2 – 24 ml
2 ml/feed	2 hourly	24 ml	24 ml
0.5-1 ml/kg/feed	1 – 2 hourly	12 – 24 ml/kg	9 – 18 ml
1 ml/kg/feed	1 – 12 hourly	2 – 24 ml/kg	1.5 – 18 ml
3 – 10 ml/kg/day	1 – 4 hourly	3 – 10 ml/kg	2.25 – 7.5 ml
10 ml/kg/day	Hourly	10 ml/kg	7.5 ml
10 – 20 ml/kg/day	1 – 6 hourly	10 – 20 ml/kg	7.5 – 15 ml
20 ml/kg/day	Hourly	20 ml/kg	15 ml
12 – 24 ml/kg/day	Not stated	12 – 24ml/kg	9 – 18 ml
20 – 40 ml/kg/day	1 – 3 hourly	20 – 40 ml/kg	15 – 30 ml
30 ml/kg/day	Not stated	30 ml/kg	22.5 ml
60 ml/kg/day	1 – 3 hourly	60 ml/kg	45 ml
60 – 90 ml/kg/day	Not stated	60 – 90 ml/kg	45 – 67.5 ml

7.7 Factors influencing clinicians' decisions

Twenty-nine factors were chosen that had previously been suggested either as having an influence on the occurrence of NEC or as issues that were commonly taken into account by clinicians when making decisions about initiation or advancement of enteral feeds. Twenty-three of these factors were also likely to be associated with the temporary discontinuation of feeds.

Factors included fell broadly into five categories:

1. Indicators of antenatal or perinatal foetal compromise (IUGR, abnormal antenatal umbilical artery Doppler studies, evidence of perinatal asphyxia);
2. Indicators of severity of illness (hypotension, suspected systemic sepsis, acidosis, use of inotropic support);

3. Indicators of respiratory compromise (mechanical ventilation or nasal continuous positive airways pressure (nCPAP), increasing oxygen requirement, recent extubation, respiratory disease in a non-ventilated infant);
4. Indicators of abdominal pathology (abdominal distension, large or bilious gastric aspirates or vomiting, blood in the stools or abdominal tenderness, failure to pass meconium);
5. Other specific factors that have been associated with NEC or feed intolerance (presence and position of umbilical catheters, sedation or pharmacological paralysis, treatment with indomethacin, blood transfusion and polycythaemia).

Clinicians were asked whether each of the chosen factors would lead them to (i) delay starting enteral feeds, (ii) slow the rate of increase of feeds and (iii) temporarily discontinue enteral feeds. It is recognised that, in practice, decision-making about changes in approach to the care of any individual baby will usually involve consideration of the condition of the baby as a whole and the package of care offered. However, many feeding-related factors have been suggested as significantly associated with important outcomes and as such may, in isolation, influence the decisions taken. Clinicians were also given the opportunity to suggest in free text, any other factors that they believed to be important in making such decisions. Four clinicians clarified their response by stating that they would rarely make decisions based on one factor in isolation, but after assessing the general condition of the baby.

Each of the factors included was considered important in decision-making by at least two clinicians. Some factors were highlighted much more frequently and consistently than others with the percentage of positive responses for an individual item ranging from 2-94%. In addition, there were differences between opinions of UK and Canadian clinicians in some areas. The responses are tabulated in Tables 7.11 to 7.14. Those factors that were considered important by more than 50% of respondents in either country are discussed below.

7.7.1 Introduction of enteral feeds

7.7.1.1 Indicators of antenatal or perinatal fetal compromise

The majority (>75%) of clinicians indicated that they would delay feeding if there was clinical evidence of perinatal asphyxia. However, 93% of Canadians would delay feeds, compared with 75% in the UK (χ^2 test, P=0.007). UK clinicians were more likely than their

Canadian counterparts to report delaying feeds on the basis of abnormal umbilical arterial Doppler studies, and in particular if reversed end diastolic flow is seen (79% versus 41%; χ^2 test, P<0.001). Absent end diastolic flow was considered less important by both groups, but the difference between the countries remained significant (58% compared with 32% (χ^2 test, P=0.001). Although abnormal antenatal umbilical Dopplers are closely related to IUGR, only 24% of clinicians overall indicated that they would delay introducing feeds because of IUGR in isolation. The difference between the UK (22.1%) and Canada (34.1%) was not statistically significant (χ^2 test, P=0.125).

7.7.1.2 Indicators of severity of illness

Hypotension requiring inotropic support is a reasonable indicator of severe illness. Almost 90% of Canadian clinicians stated that they would do so in a hypotensive baby compared with 65% UK clinicians (χ^2 test, P=0.002). Sixty-eight percent of Canadians versus 46% of UK clinicians indicated that they would delay feeding if inotropic drugs were required (χ^2 test, P=0.006). There was a smaller, but still statistically significant difference between the two countries' clinicians in the case of suspected sepsis (χ^2 test, P=0.044).

7.7.1.3 Indicators of respiratory compromise

Half of all Canadian respondents indicated that respiratory disease in a non-ventilated baby was a reason to delay initiation of feeds compared with only 36% of UK clinicians. This difference was not statistically significant.

Recent extubation was highlighted by just over 50% of clinicians. In addition, clinicians were asked to indicate the length of time for which feeds would be withheld after extubation. 138 clinicians responded and durations for which feeds were withheld varied considerably. The commonest responses were 2-4 hours (n=81) and 6-12 hours (n=44). However, 8 clinicians would delay for <2 hours and 2 clinicians for >24 hours. No other indicators of respiratory illness were consistently identified by > 32% of clinicians in either group.

Table 7.11: Reasons for delaying initiation of enteral feeds

	No. (%) clinicians who would delay enteral feeding		
	UK (n=258)	Canada (n=44)	Total (n=302)
History of absent end diastolic flow	149 (57.8)	14 (31.8)	163 (54.0)
History of reversed end diastolic flow	204 (79.1)	18 (40.9)	222 (73.5)
Evidence of perinatal asphyxia	193 (74.8)	41 (93.2)	234 (77.5)
Presence of UVC	44 (17.1)	4 (9.1)	48 (15.5)
Presence of UAC	48 (18.6)	9 (20.5)	57 (18.9)
Position of UAC	33 (12.8)	6 (13.6)	39 (12.9)
Hypotension	168 (65.1)	39 (88.6)	207 (68.5)
Suspected systemic sepsis	116 (45.0)	27 (61.4)	143 (47.4)
Sedation	7 (2.7)	6 (13.6)	13 (4.3)
Nasal CPAP	15 (5.8)	6 (13.6)	21 (7.0)
Respiratory disease (not ventilated)	92 (35.7)	22 (50.0)	114 (37.7)
Acidosis	62 (24.0)	18 (40.9)	80 (26.5)
Pharmacological paralysis	74 (28.7)	28 (63.6)	102 (33.8)
Failure to pass meconium	30 (11.6)	5 (11.4)	35 (11.6)
Polycythaemia	51 (19.8)	3 (6.8)	54 (17.9)
IUGR	57 (22.1)	15 (34.1)	72 (23.8)
Mechanical ventilation	47 (18.2)	14 (31.8)	61 (20.2)
Increasing inspired oxygen	64 (24.8)	10 (22.7)	74 (24.5)
Treatment with indomethacin	79 (30.6)	32 (72.7)	111 (36.8)
Use of inotropes	118 (45.7)	30 (68.2)	148 (49.0)
Mild abdominal distension	54 (20.9)	4 (9.1)	58 (19.2)
Severe abdominal distension	243 (94.2)	41 (93.2)	284 (94)
Bloody stools	235 (91.1)	39 (88.6)	274 (90.7)
Abdominal tenderness	232 (89.9)	38 (86.4)	270 (89.4)
Large gastric aspirates	178 (69.0)	22 (50.0)	200 (66.2)
Bilious gastric aspirates	224 (86.8)	36 (81.8)	260 (86.1)
Vomiting	159 (61.6)	32 (72.7)	191 (63.2)
Recent extubation	133 (51.6)	20 (45.5)	153 (50.7)
Blood transfusion	16 (6.2)	0	16 (5.3)

7.7.1.4 Indicators of abdominal pathology

Potential indicators of abdominal pathology were the factors most commonly identified by clinicians as likely to lead to a delay in the introduction of enteral feeds, with severe abdominal distension, the presence of blood in the stools, abdominal tenderness and bilious gastric aspirates each influencing >80% of clinicians in both the UK and Canada. Vomiting would lead >60% of UK and Canadian clinicians to delay feeding. The presence of large gastric aspirates was considered important by 69% of UK clinicians and 50% of Canadian clinicians, representing a significant difference between the two groups (χ^2 test, P=0.014).

7.7.1.5 Other factors

There were highly significant differences between the numbers of clinicians in Canada and the UK who considered the use of indomethacin and the use of pharmacological paralysis as reasons to delay the introduction of enteral feeding. Seventy-three percent of Canadian clinicians would delay feeding with indomethacin, compared with 31% in the UK (χ^2 test, P<0.001) and 64% compared with 29% would delay feeding in a baby treated with muscle relaxants (χ^2 test, P<0.001). No data were obtained with respect to whether clinicians favoured giving short or prolonged courses of indomethacin or whether it was used prophylactically.

7.7.2 Progression of enteral feeds

7.7.2.1 Indicators of antenatal or perinatal fetal compromise

In babies where a clinical decision has been taken to begin enteral feeding, the most commonly identified reason overall (81% clinicians) for slow advancement of feeds was a history of reversed end diastolic flow on antenatal Doppler studies. However, in this and in cases of absent end diastolic flow, clinicians in the UK were more likely to report a cautious approach to feeding (86% and 70.5% compared with 52% and 41% respectively (χ^2 test, P<0.001 for both)). Most Canadian (84%) and UK (70.5%) clinicians would advance feeds more slowly if there was evidence of perinatal asphyxia. 61% of Canadian clinicians but only 42% of UK clinicians indicated that they would feed more slowly in growth restricted babies (χ^2 test, P=0.028).

7.7.2.2 Indicators of severity of illness

Overall, 55% would feed more slowly in hypotensive infants, with a slightly, but not significantly increased tendency in Canada. 59% of Canadian, but only 40% UK clinicians would do so if inotropic support were required (χ^2 test, P=0.027).

7.7.2.3 Indicators of abdominal pathology

Between 50% and 75% of clinicians would slow the rate of increase of feeds if the baby displayed any of the signs of potential intra-abdominal pathology, and there was agreement between groups from both countries. Large gastric residual volumes and vomiting were most commonly identified.

7.7.2.4 Other factors

As seen with the introduction of feeds, there was a significant difference between clinicians in the UK and those in Canadian units regarding the importance of treatment with indomethacin when making feeding-related decisions, with 66% of Canadian, compared with 39.5% UK clinicians feeding more slowly (χ^2 test, P=0.002).

Table 7.12: Reasons for slowing the rate of increase of enteral feeds

	No. (%) clinicians who would slow the rate of increase of enteral feeds		
	UK (n=258)	**Canada (n=44)**	**Total (n=302)**
History of absent end diastolic flow	182 (70.5)	18 (40.9)	200 (66.2)
History of reversed end diastolic flow	222 (86.0)	23 (52.3)	245 (81.1)
Evidence of perinatal asphyxia	182 (70.5)	37 (84.1)	219 (72.5)
Presence of UVC	55 (21.3)	6 (13.6)	61 (20.2)
Presence of UAC	71 (27.5)	9 (20.5)	80 (26.5)
Position of UAC	37 (14.3)	6 (13.6)	43 (14.2)
Hypotension	135 (52.3)	30 (68.2)	165 (54.6)
Suspected systemic sepsis	119 (46.1)	20 (45.5)	139 (46)
Sedation	14 (5.4)	7 (15.9)	21 (7.0)
Nasal CPAP	35 (13.6)	10 (22.7)	45 (14.9)
Respiratory disease (not ventilated)	91 (35.3)	21 (47.7)	112 (37.1)
Acidosis	49 (19.0)	12 (27.3)	61 (20.2)
Pharmacological paralysis	63 (24.4)	20 (45.5)	83 (27.5)
Failure to pass meconium	74 (28.7)	8 (18.2)	82 (27.2)
Polycythaemia	54 (20.9)	9 (20.5)	63 (20.9)
IUGR	109 (42.2)	27 (61.4)	136 (45)
Mechanical ventilation	53 (20.5)	8 (18.2)	61 (20.2)
Increasing inspired oxygen	88 (34.1)	13 (29.5)	101 (33.4)
Treatment with indomethacin	102 (39.5)	29 (65.9)	131 (43.4)
Use of inotropes	103 (39.9)	26 (59.1)	129 (42.7)
Mild abdominal distension	134 (51.9)	20 (45.5)	154 (51.0)
Severe abdominal distension	161 (62.4)	27 (61.4)	188 (62.3)
Bloody stools	143 (55.4)	27 (61.4)	170 (56.3)
Abdominal tenderness	140 (54.3)	25 (56.8)	165 (54.6)
Large gastric aspirates	180 (69.8)	33 (75.0)	213 (70.5)
Bilious gastric aspirates	151 (58.5)	27 (61.4)	178 (58.9)
Vomiting	173 (67.1)	32 (72.7)	205 (67.9)
Recent extubation	66 (25.6)	7 (15.9)	73 (24.2)
Blood transfusion	16 (6.2)	0	16 (5.3)

7.7.3 Temporary discontinuation of enteral feeds

The only reasons commonly identified for discontinuing feeds by both groups of clinicians were indicators of abdominal pathology and in particular, those signs that might be present in a baby with suspected NEC. These included severe abdominal distension, bloody stools and abdominal tenderness, which were identified by approximately 90% of clinicians in both countries as reasons to discontinue enteral feeds. Bilious or large aspirates were also regarded as indicators to stop enteral feeds, but by smaller numbers of clinicians in both countries (73% and 82% respectively). The only other factor identified as an indication to stop feeds was hypotension, by 52% of Canadian clinicians, but by only 34% in the UK (χ^2 test, P=0.028).

7.7.4 Significance of acidosis

Clinicians who indicated that acidosis would be an influencing factor in decision-making were also asked to suggest a level of acidosis that they would consider significant. Eighty (26%) responses suggested that acidosis would affect feed initiation, although less than three quarters of these clinicians provided an opinion about significant levels of acidosis. Similarly, although positive responses were received from 49 (16%) and 61 (20%) clinicians respectively in response to questions about feed advancement and discontinuation respectively, 40% and 30% of these respondents respectively did not offer opinions regarding levels. Three UK clinicians suggested significant levels of acidosis, but indicated that acidosis would not influence their decision-making.

Although less than 50% of clinicians stated that this was an important factor for any aspect of feeding, there was variation between the responses received. This variation encompassed differences in the measurements used to assess the degree of acidosis as well as differences in the values considered significant. For each of the three aspects of feeding, there were between eight and ten different responses regarding the level that might be used clinically as a "cut-off point" to indicate significant acidosis; these are summarised in Table 7.13. However, the most commonly used levels were a pH of <7.2 or 7.25. This was consistent across the three areas of feeding practice and for both UK and Canadian subgroups.

Table 7.13: Level of acidosis considered sufficiently significant to influence decisions about feeding

	Feed initiation Number (%) clinicians n=65	**Feed advancement** Number (%) clinicians n=43	**Feed discontinuation** Number (%) clinicians n=31
pH			
< 7.0	5	2	4
< 7.1	4	4	5
< 7.15	1	1	0
< 7.2	23 (35%)	15 (35%)	7 (23%)
< 7.25	18 (28%)	13 (30%)	7 (23%)
< 7.3	2	1	1
Base excess			
> -15	3	1	1
> -12	1	0	0
> -10	4	3	3
Lactate >2	1	1	0
Increasing acidosis	1	1	2
Unable to quantify	2	1	1

Figure 7.14: Reasons for temporary discontinuation of enteral feeds

	No. (%) clinicians who would discontinue enteral feeds		
	UK (n=258)	Canada (n=44)	Total % (n=302)
Hypotension	87 (33.7)	23 (52.3)	110(36.4)
Suspected systemic sepsis	94 (36.4)	20 (45.5)	114 (37.7)
Sedation	9 (3.5)	3 (6.8)	12 (4.0)
Nasal CPAP	5 (1.9)	0	5 (1.7)
Respiratory disease (not ventilated)	39 (15.1)	5 (11.4)	44 (14.6)
Acidosis	41 (15.9)	8 (18.2)	49 (16.2)
Pharmacological paralysis	54 (20.9)	21 (47.7)	75 (24.8)
Failure to pass meconium	25 (9.7)	11 (25.0)	36 (11.9)
Polycythaemia	13 (5.0)	0	13 (4.3)
IUGR	6 (2.3)	0	6 (2.0)
Mechanical ventilation	24 (9.3)	0	24 (7.9)
Increasing inspired oxygen	43 (16.7)	2 (4.5)	45 (14.9)
Treatment with indomethacin	45 (17.4)	18 (40.9)	63 (20.9)
Use of inotropes	71 (27.5)	18 (40.9)	89 (29.5)
Mild abdominal distension	30 (11.6)	1 (2.3)	31 (10.3)
Severe abdominal distension	236 (91.5)	39 (88.6)	275 (91.1)
Bloody stools	233 (90.3)	41 (93.2)	274 (90.7)
Abdominal tenderness	230 (89.1)	40 (90.9)	270 (89.4)
Large gastric aspirates	188 (72.9)	33 (75.0)	221 (73.2)
Bilious gastric aspirates	214 (82.9)	34 (77.3)	248 (82.1)
Vomiting	125 (48.4)	26 (59.1)	151 (50.0)
Recent extubation	113 (43.8)	15 (34.1)	128 (42.4)
Blood transfusion	25 (9.7)	0	25 (8.3)

7.7.5 Significance of gastric residual volumes

Clinicians indicating that large volume gastric aspirates would influence their decision-making were also asked to state the volume that they considered "large". Although this was commonly identified as a reason for delaying introduction (66%), slowing advancement

(70%) and discontinuing (73%) enteral feeds, responses to this part of the question were fewer. Of those responding to the first part of each question, only 56%, 52% and 45% (113, 112 and 100 clinicians respectively for the 3 aspects of feeding) chose to state what they perceived as "large". There was a great variation in responses with respect to volumes of aspirate stated and how these were measured. Clinicians variably expressed volumes as absolute volumes of between 1ml and 10ml, volumes over a time period (1-2ml/hour, 5-10ml/4 hours) or by body weight (1-10ml/kg, ml/kg/day or ml/kg/hour). The most common measure was expressed as a percentage of feed volumes given but this varied from 20% to 100% of the volume of milk given. There were over 30 different measures suggested, with no single measurement identified by more than 22 clinicians. The most frequent responses for all three questions were 2ml, 5ml, 50% and 100% of feed volume.

7.8 Decision-making with respect to feed discontinuation

Clinicians were asked to identify which groups of staff most often make decisions about discontinuation of feeds in their NNU. Taking into account the differences in NNU personnel and nomenclature between the UK and Canada, different lists were used for each country. There were 256 responses from UK clinicians and 44 from Canadian clinicians.

7.8.1 United Kingdom

There was great variation in responses, with 18 different combinations of staff identified and agreement between responses from only 6 UK NNUs. Bedside nurses alone were reported to make most of the decisions by 36 individual clinicians, consultants by 12 clinicians and middle grade doctors by 19 clinicians. However, combining responses from clinicians by NNU indicated that in most NNUs (109/135 (80%)), decisions were taken by a combination of nursing and medical staff. Consultants were said to be involved in decision-making in all but one of these units. In 22/135 (16%), medical staff only were reported to make decisions and in 5/135 (4%), nursing staff only. SHOs were the group of staff least often involved (38/135 (28%)) and middle grade doctors most commonly (121/135 (90%)). Members of the nursing staff were involved in decisions to stop feeds in 114/135 (84%) units. Neonatal nurse practitioners were involved in 55/135 (41%) units.

7.8.2 Canada

In Canada, decisions were also most often made by a combination of medical and nursing staff. Two units reported that the attending neonatologist made these decisions and no unit reported that decisions were mostly taken by nursing staff alone. Nurses were involved in decisions in 9/17 (53%) units and neonatal nurse practitioners in 11/17 (65%) units. Fellows and residents were involved in 13/17 (76%) and 14/17 (82%) units respectively. Attending neonatologists were involved in 14/17 (82%) units.

PART III

RETROSPECTIVE REVIEW OF MEDICAL RECORDS

CHAPTER 8

STUDY METHODS

8.1 Data

8.1.1 Data collection

Data were collected for all babies born with a gestational age of <30 weeks and/or a birth weight of ≤ 1500g and admitted to selected NNUs within a defined period of time. The six months between 1 February and 31 July 2004 was chosen, as all babies born during this time period had been discharged from inpatient hospital care and therefore medical records would be likely to be complete and available for detailed review. Collection of data was designed to identify babies at highest risk of feeding-related complications, by virtue either of low gestational age or of IUGR.

Following central ethics approval, neonatologists in all UK centres to be included in the retrospective review of records were approached by letter in order to ascertain whether they were willing for their neonatal unit to participate. When clinicians had confirmed their intention for their unit to participate, the Human Resources department for each relevant hospital trust was contacted, initially by telephone and then by letter to the appropriate member of staff to establish the required procedures for obtaining permission to collect data as an outside researcher entering the trust. Procedures and the time taken to meet requirements varied considerably between trusts, with most requiring an honorary contract of employment to be issued for the duration of the research within that location. In total, seventeen UK trusts were approached. However, access for research was gained in only fifteen, as one trust provided the contract too late for the research to be performed and another was unwilling to allow the study to proceed without consent from all parents of infants.

In Canada, similar processes were followed, but ethics approval was required for each single centre. Although five centres were approached, the time-consuming nature of the ethics approval process meant that only three centres could be included in the study.

A local contact within the neonatal service in each participating centre was identified to facilitate data collection. In some units, this was a neonatologist and, in others, an administrative assistant or research nurse. In addition, these contacts were instrumental in giving guidance about local processes for identifying eligible infants and obtaining the relevant medical records. It was also necessary to arrange convenient times to visit the neonatal units, when records would be available and when a suitable place on site could be identified for review of the records. Medical and nursing records of all babies born with a gestational age of <30 weeks and/or a birth weight of ≤ 1500g and admitted to the selected NNUs during this period of time were requested. All available paper and electronic medical and nursing records and nursing charts for the whole of the neonatal hospital stay were reviewed in detail by a single researcher (EMB). Data collection took place over a number of days for each participating unit, at the convenience of both researcher and clinicians.

Feeding data were collected from birth until two weeks after the attainment of full enteral feeds. Data for clinical conditions or areas of practice that might be expected to influence feeding practice were also collected for this period of time, but no data were collected for doses of drugs such as morphine and indomethacin. Analysis of the effects of these factors on clinical practice was guided by the literature review and information from responses of clinicians in the first part of the survey. Data items are listed in Appendix 3.

8.1.2 Data analysis

Data were analysed using SPSS for Windows Version 16.0.2 (SPSS Inc 1989-2007). Comparisons of proportions were analysed using Chi-squared tests. Comparisons between continuous variables were made using independent samples t-tests for normally distributed data with presentation of means (SDs) or Mann Whitney U tests for non-parametric data, presented with medians (interquartile ranges). Distributions of all continuous data were examined for normality using graphical measures (histograms, normality plots) and Shapiro-Wilk tests of normality. A number of variables were not normally distributed, including the day of first feed and time to full feeds. In these cases where continuous variables were not normally distributed, data were transformed for analysis using log10 transformation to obtain a more normal distribution. Data were presented as geometric means and variation between

centres was analysed using one-way analysis of variance (ANOVA). Adjustments for multiple comparisons were made using the Bonferroni method.

Relationships between variables were analysed using multiple regression analysis for continuous outcome variables and binary logistic regression for binary categorical outcome variables. Initially, univariate analyses were performed to assess the strength of relationship between potentially relevant independent variables and outcome variables. Those that showed an association ($P < 0.2$) were entered into the multivariate regression models. This P value was chosen to ensure that all those showing some association, even if not statistically significant, would be included in further analysis. In all multivariate regression models, independent variables were entered simultaneously. Variables were retained in the model if they showed an independent association with the outcome variable ($P<0.1$). This P value was chosen to ensure inclusion of all those factors with most significant associations. P values of <0.05 were considered significant for all statistical tests.

All infants of <30 weeks of gestation were included in the study, whereas more mature infants were only included if they met the study birth weight criterion of ≤1500g. This allowed inclusion of some more mature, but growth-restricted babies and analysis of data by either birth weight or gestation as appropriate. Inclusion criteria were the same for both countries. For analyses according to gestational age or birth weight, babies were divided into groups. For gestational age these groups were (i) <26 weeks+0 days; (ii) 26-27 weeks+6 days; (iii) 28-29 weeks+6 days, and (iv) ≥ 30 weeks. Groups were selected to most closely reflect clinical differences related to maturity and boundaries often chosen by clinicians when considering the effects of immaturity. In order to reflect current reported practice with respect to guidelines based on birth weight, the group was divided into three groups for some of the analysis: (i) <1000g; (ii) 1000-1249g; (iii) >1250g.

8.2 Neonatal Units

Units included in the retrospective review were chosen based on a pragmatic approach. To ensure that it would be feasible to complete data collection, units were chosen in parts of the UK that were easily accessible and where accommodation was available for the researcher. These fell into two main geographical areas – Scotland and the middle of England. Although ideally the whole of the UK would have been included or a random sample selected from

across the whole country, this was judged to be impractical given the limited time available for data collection. It is possible that this decision will have introduced an element of selection bias because of regional training methods or guidelines. However, the units visited were spread over a large geographical area and encompassed a number of different regions for training and service provision. The area served by the units also comprised urban and rural populations, minimising bias due to population characteristics. It is unlikely that there are large systematic differences between these and the remaining regions of the UK that were not included. It was also considered important that units of differing sizes were included to produce a more representative sample.

NNUs that were included in Canada were those that were geographically accessible and were able to grant ethical approval within the limited time available of one year. All three NNUs were located in the region around Toronto in Ontario. It is acknowledged that these three units may not be representative of neonatal practice throughout the whole of Canada. However, the area served by these three NNUs is large and covers both urban and rural regions.

8.3 Infants

A total of 701 babies were identified as having been born during the six-month period chosen for the survey. The medical and nursing records of 695 babies in 18 NNUs (15 UK units and 3 Canadian units) were examined. Data for a further six babies were not included because data were not available. Reasons for this included inability to locate medical records within the hospital and medical notes being needed by other authorities at the time they were requested for review.

8.3.1 Exclusions

In total, 25 infants whose records had been reviewed were excluded from the final data analysis. This was due either to crucial data being unavailable or to specific factors that rendered the babies inappropriate for inclusion. The reasons for exclusion are detailed below. Excluded infants were of significantly lower birth weight, were sicker as determined by CRIB score and were more likely to die than included infants (Table 8.2).

8.3.1.1 Exclusions due to gestational age and birth weight

Both in the UK and in Canada, it is unusual for resuscitation to be initiated at birth for infants born before 23 weeks of gestation or with a birth weight of less than 450g. One infant in the group was born at 22 weeks and another at 21 weeks of gestation. A further two infants were born with birth weight of less than 450g. All infants survived for only a short time after birth and were never fed. Since these infants were felt not to be representative of the preterm population generally cared for in NNUs in either country, all four infants were excluded.

8.3.1.2 Exclusions due to congenital anomalies

Of the 695 babies included in the review, 17 (2.4%) had congenital anomalies. These are listed in Table 8.1. Of these, three had recognised lethal anomalies and a further four had major anomalies that would be likely to require early surgical management and therefore would be expected to significantly affect feeding of these infants. Data for these seven infants were therefore excluded from analysis.

8.3.1.3 Exclusions due to missing data

Birth weight was missing for one infant and gestational age at birth for another. These infants were excluded, as further analysis would not be possible without this information.

For two infants, nursing charts documenting data relating to feed volumes for the whole of the neonatal stay were unavailable. A further ten infants had substantial amounts of feeding data missing from records due to being transferred from or to another hospital, making it impossible to determine times of starting feeds or attaining full enteral feeds. These infants were also excluded. Infants who were transferred, but for whom this information was available were not excluded, but were not included in analyses where detailed information about feeding volumes were required.

Table 8.1: Types of congenital anomalies and exclusions

Nature of anomaly	Number of babies affected	Excluded
Unilateral absent radius	1	No
Ambiguous genitalia	1	No
Severe airway anomaly	1	Yes
Hydronephrosis	1	No
Choanal atresia	1	Yes
Congenital diaphragmatic hernia	1	Yes
Donohue syndrome	1	Yes
Hypoplastic left heart syndrome	1	Yes
Coarctation of aorta	1	Yes
Peters anomaly of the eye	1	No
Pierre Robin sequence (mild)	1	No
Trisomy 13	1	Yes
Trisomy 2 mosaicism	1	No
Trisomy 21	2	No
Cystic kidney(s)	2	No

Table 8.2: Comparison between included and excluded infants

	Included n=670	Excluded n=25	Significance (P value)
Birth weight (g)	1120 (913-1315)	1010 (625-1150)	0.009
Gestation (weeks)	28 (27-30)	28 (26-31)	0.513
IUGR < 10th centile , n (%)	208 (31.0)	12 (48.0)	0.116
CRIB score	2 (1-5)	6 (2-8)	0.005
5 minute Apgar score	9 (8-9)	8 (7-9)	0.297
Deaths, n (%)	75 (11.2)	7 (28.0)	0.02

Values for continuous variables presented as median (interquartile range);

Values for categorical variables are presented as n (%);

Mann-Whitney U test for comparison between continuous variables;

χ^2 test for comparison between categorical variables.

CHAPTER 9

RESULTS

9.1 Characteristics of study infants

Characteristics of the infants included in the study are summarised in tables 9.1 and 9.2. There was a significant difference between the UK and Canadian groups of babies for gestation at birth and a non-significant difference for birth weight and all other comparisons.

Table 9.1: Infant characteristics

	Total n=670	**UK n=451**	**Canada n=219**	**P value**
Birth weight (g)	1120 (913-1315)	1145 (945-1320)	1080 (860-1310)	0.065
Gestation (weeks)	28 (27-30)	28 (27-30)	28 (27-30)	0.024
Male sex, n (%)	337 (50.3)	230 (51.0)	107 (48.9)	0.662
IUGR < 10th centile, n (%)	208 (31.0)	148 (32.8)	60 (27.4)	0.183
CRIB score	2 (1-5)	2 (1-4)	2 (1-6)	0.401
5 minute Apgar	9 (8-9)	9 (8-9)	8 (7-9)	0.586
Deaths, n (%)	75 (11.2)	54 (12.0)	21 (9.6)	0.431

Values for continuous variables presented as median (interquartile range);

Values for categorical variables are presented as n (%);

Test of normality (Shapiro-Wilk): P<0.001 for each variable;

Mann Whitney U test for continuous variables; χ^2 test for categorical variables.

9.1.1 Gestational age

Gestational ages of UK babies ranged from 23-37 weeks, with 10 babies born at >35 weeks, whereas the range for Canadian babies was 23-34 weeks, with only five babies born after 32 weeks and none at >34 weeks; although the median gestational age was similar for both countries, there was a significant difference between the two. There were only six infants born before 24 weeks of gestation.

Table 9.2: Number and characteristics of infants by unit

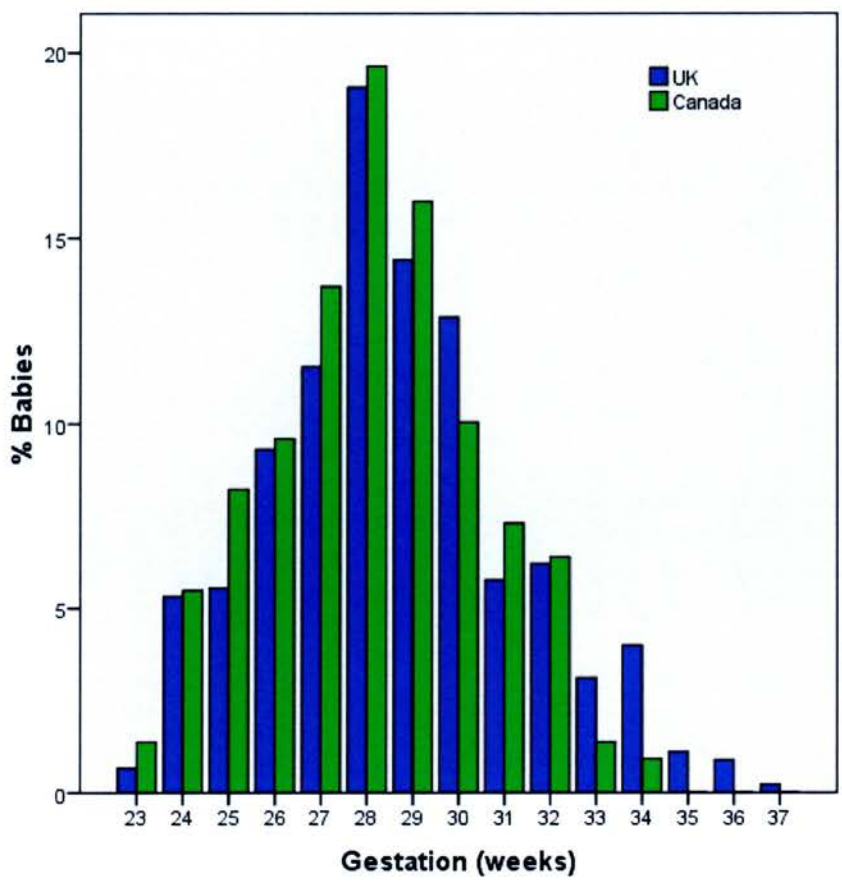
Unit	Country	No. of infants	Gestation (weeks)	Birth weight (grams)
1	UK	56	28 (26-30)	1135 (916-1315)
2	UK	17	28 (27-29)	1090 (835-1335)
3	UK	6	29.5 (27-34)	1210 (1110-1480)
4	UK	30	28 (27-29)	1190 (1027-1350)
5	UK	50	28.5 (27-30)	1130 (887-1305)
6	UK	42	28 (27-30)	1187.50 (1053-1323)
7	UK	20	28 (26-30)	1140 (982-1252)
8	UK	43	28 (27-30)	1080 (955-1290)
9	UK	15	29 (28-30)	1210 (1025-1365)
10	UK	59	29 (27-31)	1100 (858-1298)
11	UK	12	29 (25-30)	1172.50 (1025-1437)
12	Canada	90	28 (27-30)	1145 (919-1334)
13	Canada	117	28 (26-29)	1040 (847-1307)
14	Canada	12	25.5 (24-28)	828.50 (597-1037)
15	UK	19	28 (25-32)	1056 (718-1456)
16	UK	13	28 (26-31)	1120 (1005-1390)
17	UK	20	29 (28-32)	1095 (1000-1287)
18	UK	49	28 (27-30)	1165 (857.50-1330.50)
Total		670		

Birth weight and gestation presented as median (interquartile range)

Table 9.3: Gestation by country

Gestation (weeks)	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
UK (n)	3	24	25	42	52	86	65	58	26	16	28	14	5	4	1
Canada (n)	3	12	18	21	30	43	35	22	16	14	3	2	0	0	0
Total by group n (%)	85 (12.7)			145 (21.6)		229 (34.2)		211 (31.5)							

Figure 9.1: Bar chart to show the proportion of babies in the UK and Canada for each week of gestation



9.1.2 Birth weight

All infants with a birth weight ≤1500g were included, to represent the population of very low birth weight infants. Since all infants of <30 weeks were also included, there were a number of babies with birth weight >1500g. The majority (63%) of included babies had birth weights between 1000g and 1500g. There were a greater proportion of Canadian babies in the lowest birth weight group.

Table 9.4: Birth weight by country

Birth Weight (g)	<1000g	1000-1249g	1250-1499	>1500	Total
UK	134	157	147	13	451
n (%)	(29.7)	(34.8)	(32.6)	(2.9)	
Canada	90	60	61	8	219
n (%)	(41.1)	(27.4)	(27.9)	(3.6)	

9.2 Significant morbidities

Several babies suffered significant morbidities during their neonatal stay. These included unilateral or bilateral intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL), seizures, pulmonary haemorrhage, pneumothorax, retinopathy of prematurity, chronic lung disease, defined as oxygen requirement persisting until 36 weeks of gestation and necrotising enterocolitis. Table 9.5 shows the proportions of infants experiencing morbidities. Some infants experienced multiple morbidities. Necrotising enterocolitis is not included and is discussed in detail in a later section.

Table 9.5: Infants experiencing significant morbidity in the UK and Canada

Condition	UK (n=451)	Canada (n=219)	Total (n=670)
Intraventricular haemorrhage			
(unilateral or bilateral; highest grade)			
Grade 1	41 (9)	34 (15.5)	75 (11.2)
Grade 2	25 (5.5)	14 (6.4)	39 (58.2)
Grade 3	6 (1.3)	7 (3.2)	13(1.9)
Grade 4	22 (4.9)	10 (4.6)	32 (4.8)
Periventricular leukomalacia			
Unilateral	6 (1.3)	3 (1.4)	9 (13)
Bilateral	2 (0.4)	0	2 (0.3)
Seizures	8 (1.8)	6 (2.7)	14 (2.1)
Pulmonary haemorrhage	21 (4.6)	6 (2.7)	27 (3.9)
Pneumothorax	18 (4)	5 (2.3)	23 (3.4)
Retinopathy of prematurity			
Stage 1	29 (6.1)	4 (1.8)	33 (4.9)
Stage 2	18 (4)	13 (5.9)	31 (4.6)
Stage3	4 (0.9)	1 (0.4)	5 (0.75)
Chronic lung disease	63 (14)	28 (12.8)	91 (13.6)

Values are presented as n (%).

9.3 Initiation of enteral feeding

Feeding data for the first enteral feed were available for 629 (94%) infants. Forty-one (6%) infants died before being fed (Table 9.6). Only one of six infants born before 24 weeks of gestation survived to start enteral feeds, but all infants >29 weeks of gestation received some enteral feed. As expected, infants who died before starting feeds were smaller and less mature (Mann Whitney U test, P <0.001 for both) and had higher CRIB scores (P =0.001) than survivors. Within this group, >55% were hypotensive and required UAC and inotropic support, compared with <50% for the whole group overall. Sedation was used in 78%, compared with 27% of the group overall and almost 20% of this group were acidotic, compared with only 2% of the overall group, showing that these babies were sicker and required more intensive care interventions.

Table 9.6: Deaths before starting feeds by gestational age at birth

Gestation, weeks (n)	23 (6)	24 (36)	25 (43)	26 (63)	27 (82)	28 (129)	29 (100)	≥30 (211)	Total (670)
UK, n (%)	2 (67)	11 (46)	6 (24)	5 (12)	7 (13.5)	2 (2.3)	1 (1.5)	0	**34** (7.5)
Canada, n (%)	3 (100)	1 (8)	0	1 (4.8)	1 (3.3)	1 (2.3)	0	0	**7** (3.2)
Total, n (%)	5 (83)	12 (33)	6 (14)	6 (9.5)	8 (9.7)	3 (2.3)	1 (1)	0	**41 (6)**

9.3.1 Factors affecting the initiation of feeds

In the clinician survey, the majority of clinicians indicated that they believed the optimum time for introducing feeds was during the first 48 hours of life. It is therefore likely that factors identified before birth or during the first two postnatal days will exert the greatest influence on the timing of feed introduction. The occurrence of these factors during the first three days of life in UK and Canadian infants is shown in Table 9.7. There are some marked differences between the UK and Canada, with respect to the infants' condition and, more significantly, the management of infants. Significant differences were found for abnormal antenatal Doppler studies, the presence of abdominal distension, mechanical ventilation, umbilical catheters and patent ductus arteriosus, the use of sedation and indomethacin. The effects of these and other potentially important factors on the initiation of feeds are explored in the following sections.

9.3.2 Type of milk used for introduction of enteral feeds

Of the 629 infants who survived to start enteral feeds 407 (64.7%) received MEBM, 132 (21%) preterm formula, 36 (5.7%) received term formula, 33 (5.2%) DEBM and 21 (3.3%) hydrolysed formula for the first enteral feed (Figure 9.2). The use of MEBM for feed initiation varied between 45% and 75% in Canadian NNUs and between 50% and 100% in UK NNUs. In Canada, if MEBM was unavailable, all but one infant received preterm formula and this infant was fed using term formula. In contrast, in similar circumstances in the UK units, 24% received DEBM and where formula was used this was preterm (33.1%), term (26.3%) or hydrolysed formula (15.8%) (Figure 9.3). The use of milks other than EBM

for the first enteral feed was confined to the first five days of life in all but five infants, one of whom received hydrolysed protein formula and four who received preterm formula.

Table 9.7: Occurrence of factors likely to influence decisions about feeding

	Total (n=670)	UK (n=451)	Canada (n=219)	P Value
Antenatal or perinatal compromise				
Abnormal antenatal doppler studies	73 (10.9)	58 (12.9)	15 (6.8)	0.027
Absent end diastolic flow	57 (8.5)	49 (10.9)	8 (3.7)	
Reversed end diastolic flow	16 (2.4)	9 (2)	7 (3.2)	
Asphyxia (diagnosis documented in records)	3 (0.4)	3 (0.7)	0	0.553
Polycythemia	5 (0.7)	5 (1.1)	0	0.278
Respiratory compromise				
Mechanical ventilation	450 (67)	288 (63.9)	162 (74)	0.011
Nasal CPAP	310 (46.3)	217 (48.1)	116 (53)	0.273
Abdominal pathology				
Presence of UAC	297 (44.3)	177 (39.2)	120 (54.8)	<0.0005
Abdominal distension (mild)	47 (7)	43 (9.5)	4 (1.8)	<0.0005
Abdominal tenderness	1 (0.1)	1 (0.2)	0	1.00
Bilious gastric aspirates	111 (16.6)	84 (18.6)	27 (12.3)	0.052
Other factors				
Hypotension	124 (18.5)	83 (18.4)	41 (18.7)	1.00
Use of inotropic drugs	124 (18.5)	83 (18.4)	41 (18.7)	1.00
Use of opiate sedation	194 (28.9)	158 (35)	36 (16.4)	<0.0005
Acidosis	65 (9.7)	51 (11.3)	14 (6.4)	0.06
Therapeutic paralysis	20 (2.9)	17 (2.7)	3 (0.9)	0.142
PDA	43 (6.4)	17 (3.8)	26 (11.9)	<0.0005
Use of indomethacin	46 (6.8)	10 (2.2)	36 (16.4)	<0.0005

Values are presented as n (%)

Figure 9.2: Type of milk used for first enteral feed

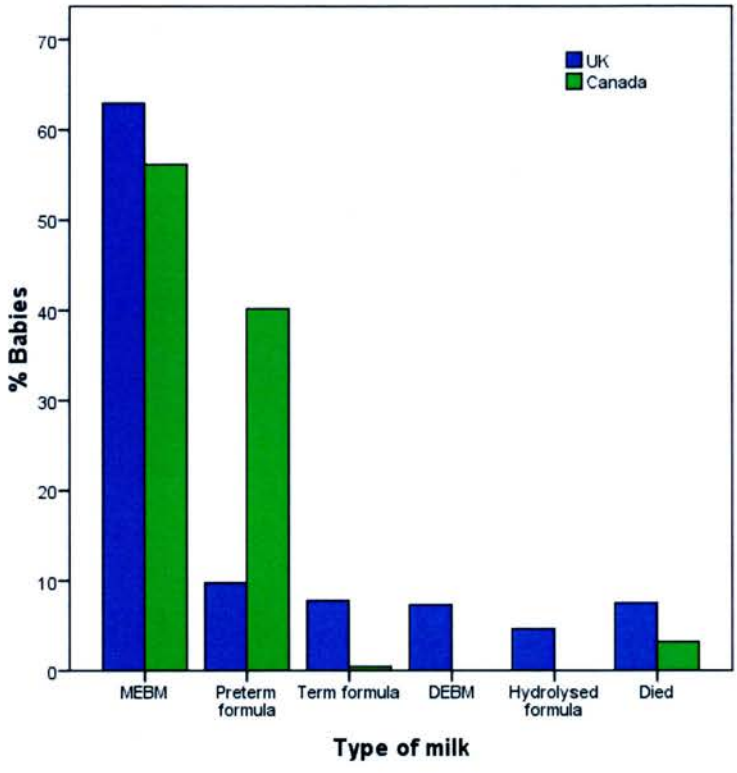
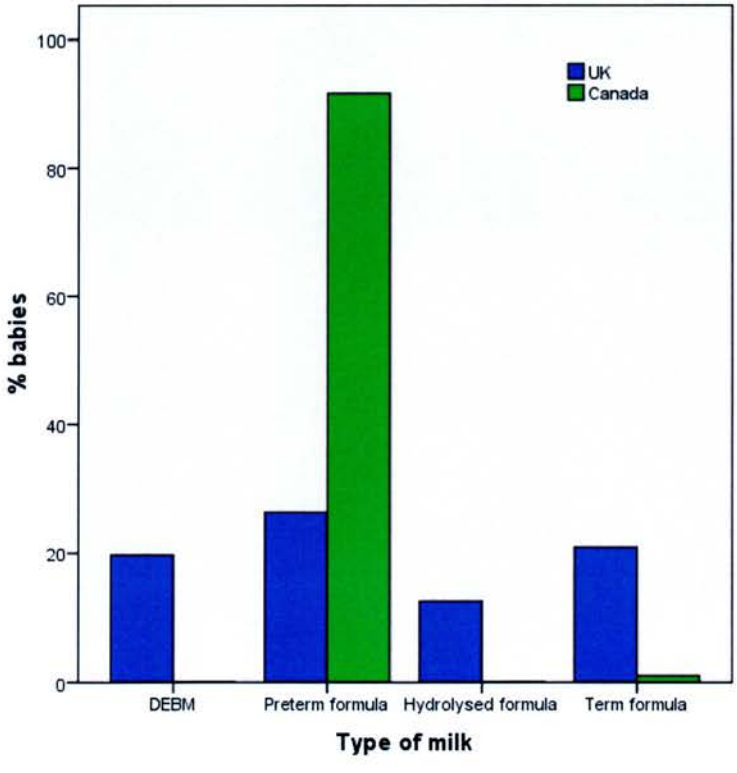


Figure 9.3: Type of milk used when MEBM not used for first enteral feed



9.3.3 Feeding methods

No infant in either country received transpyloric feeding at any time and all enteral feeds were given by either nasogastric or orogastric tube. Of the 629 infants, 91% were fed using bolus feeds. The remaining 9% received continuous feeding. Only three NNUs, all within the UK, used continuous feeding. In two of these units, this method of feeding appeared to be the norm, with over 90% babies fed in this way. In another smaller unit, 4/6 babies were continuously fed.

Most infants (497/629 (79%)) received volumes of 0.5-1 ml for feeds for their first feeds. 8% (53/629) received less than 1ml, 59/629 (9%) 1-5ml and 21 infants received more than 5ml, with the largest volume of 17ml fed to an infant of 36 weeks of gestation.

Data were available for the interval between feeds in the first two days after feed initiation for 604/629 (96%) infants. Feeds were administered hourly in 45% and every two hours in 24%. Where feeds were given at one or two hourly intervals, this was maintained for several days before increasing the interval between feeds with increasing postnatal age of the babies. The remaining babies received feeds every 3, 4, 6, 8 or 12 hours and in these the time between feeds was reduced more quickly, reaching intervals of one or two hours within a small, but variable number of days. Correlation between the volume of first feeds administered and birth weight, gestation and CRIB score were only weak (r=0.251, 0.351 and -0.151 respectively). There were similar weak correlations between feed interval and these variables (r=0.314, 0.311 and 0.263 respectively). Figure 9.4 shows a box plot of feed intervals by centre and this suggests both inter- and intra-unit variation that may be more related to other factors such as centre or clinician preference.

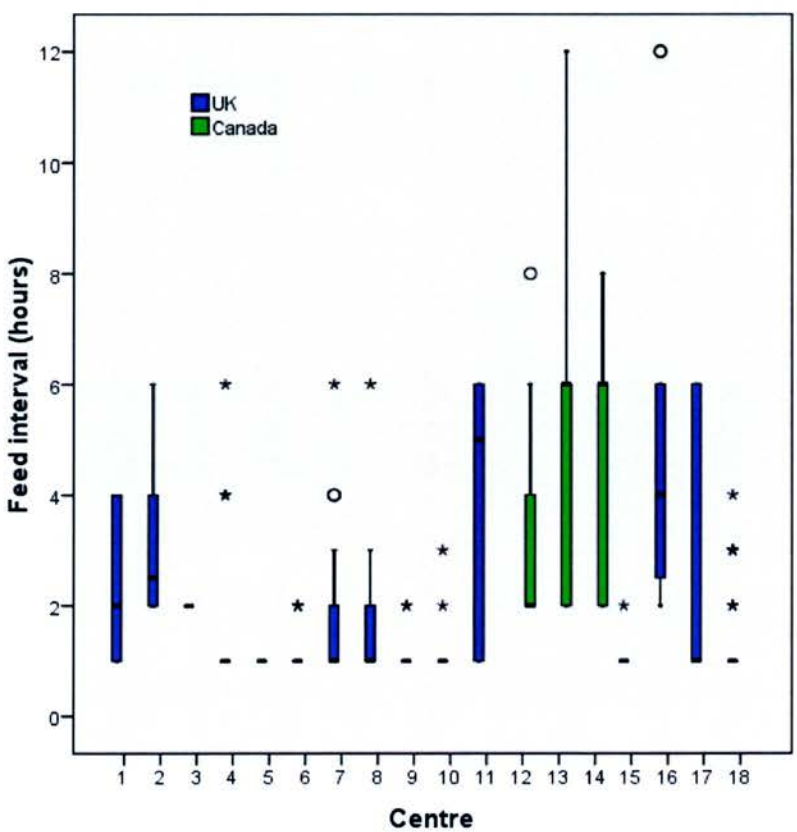
9.3.4 Timing of introduction of enteral feeds

There were 274 (44%) infants who started feeds within the first 48 hours of life and a further 153 (24%) commenced on the third day. The remaining 32% received their first enteral feed at between 4 and 14 days of life. The median (IQR) postnatal day on which enteral feeds started was Day 3 (2-4) for the whole group. Data for the day of first feed were positively skewed and were log transformed for further analysis. An independent samples *t* test was performed to compare the mean time of first feed between countries and showed a

significant difference; UK infants received the first feed 15% earlier than Canadian infants (Table 9.8). Figure 9.5 shows a box plot of the day of first feed by centre. One-way ANOVA was used to explore the differences in the geometric mean time to first feed between centres. This showed a highly significant difference between the centres (Table 9.9)

Variation in the geometric mean day of first feed between groups of infants with different gestational age and birth weight was examined using one-way ANOVA and showed a highly significant difference between groups for both (Tables 9.10 and 9.11). Adjustments for multiple comparisons were made using the Bonferroni method. Significant differences were found between all gestational age ($P < 0.02$ for each comparison) and all birth weight ($P < 0.0001$ for each comparison) groups.

Figure 9.4: Box plot to show feed interval by centre



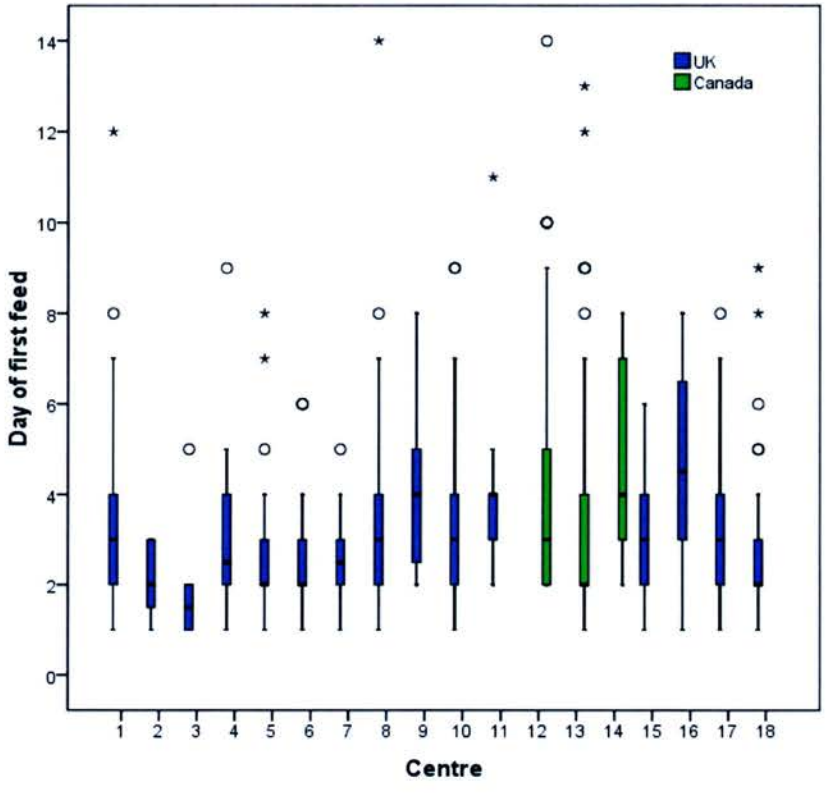
*Top and bottom of boxes represent 25th and 75th percentiles; Bar represents median; Whiskers represent smallest values that are not outliers or extreme values;° represents outliers; * represents extreme values*

Table 9.8: Comparison of day of first feed between UK and Canada

	Geometric mean (95% CI)		Ratio of geometric means (95% CI)	P value
	UK (n=417)	Canada (n=212)		
Day of first feed	2.63 (2.49, 2.77)	3.08 (2.87, 3.31)	0.85 (0.78, 0.93)	0.001

Independent samples t test; log10 transformed data

Figure 9.5: Box plot to show the day of first feed by centre



*Top and bottom of boxes represent 25th and 75th percentiles; Bar represents median; Whiskers represent smallest values that are not outliers or extreme values;° represents outliers; * represents extreme values*

Table 9.9: One-way ANOVA for mean day of first feed by centre

Centre	No. of infants	Mean day of first feed*	95% CI	P Value#
1	50	3.01	2.62, 3.47	<0.0005
2	16	1.91	1.52, 2.39	
3	6	1.65	-1.19, 3.23	
4	30	2.57	2.14, 3.09	
5	47	2.20	1.90, 2.56	
6	40	2.18	1.88, 2.53	
7	20	2.38	1.97, 2.86	
8	40	3.22	2.69, 3.87	
9	15	3.56	2.81, 4.51	
10	51	2.77	2.37, 3.25	
11	10	3.72	2.62, 5.27	
12	89	3.54	3.19, 3.92	
13	114	2.68	2.43, 2.96	
14	9	4.59	3.10, 6.78	
15	16	2.61	1.92, 3.55	
16	12	3.82	2.43, 6.00	
17	19	2.91	2.25, 3.77	
18	45	2.33	1.94, 2.79	

**geometric mean; # Significance value for difference between groups*

Table 9.10: One-way ANOVA for mean day of first feed by gestation

Gestation	No.	Mean day of first feed*	95% CI	P Value#
< 26 weeks	62	4.26	3.70, 4.89	< 0.0005
26-27 weeks	131	3.38	3.09, 3.69	
28-29 weeks	225	2.86	2.69. 3.05	
≥ 30 weeks	211	2.09	1.96, 2.24	

**geometric mean; # Significance value for difference between groups*

Table 9.11: One-way ANOVA for mean day of first feed by birth weight

Birth weight	No.	Mean day of first feed*	95% CI	P Value#
< 1000g	191	3.6	3.38, 3.91	<0.0005
1000-1249g	210	2.88	2.69, 3.08	
>1250g	228	2.14	2.00, 2.28	

**geometric mean; # Significance value for difference between groups*

9.3.4.1 Associations with the time of initiation of enteral feeds

(a) All infants

Data for all babies surviving to start feeds were analysed using multiple regression to examine other factors contributing to the variation in the time to starting enteral feeds. Factors that were considered, but that did not show an association were asphyxia and blood in the stools, but these were present in only two and four infants respectively. Abdominal tenderness was recorded as being present in only one infant and this variable was therefore not included. Mechanical ventilation, but not the use of nCPAP was significantly associated with the time of feed initiation, but 72% of babies who received nCPAP were also ventilated during the first 72 hours of life; nCPAP was therefore excluded from the model.

Independent variables were classified as present or absent during the first 72 hours of life. The following were initially entered simultaneously into the regression model, together with birth weight, gestation and CRIB score: IUGR, abnormal antenatal umbilical Dopplers, umbilical catheters, hypotension, PDA, opiate sedation, acidosis, mechanical ventilation, therapeutic paralysis, inotropic support, indomethacin, and bilious gastric aspirates. Birth weight and gestation were highly correlated (0.676) and showed strong collinearity. Hypotension and the use of inotropes were also highly correlated (0.772). Birth weight and inotropes were retained as they showed a greater contribution to the model. Other variables were retained in the model if they showed an independent association with the time to first feed ($P<0.1$) This P value is conventionally used to ensure inclusion of those factors with most significant associations.

Variables independently associated with the time to first feed were abnormal Dopplers, opiate sedation, acidosis, mechanical ventilation, inotropic support, indomethacin and birth

weight. Infants with higher birth weight were fed earlier and infants in whom other factors were present started milk feeds later. This model accounted for approximately 34% of the variation in time to first feed (r^2 0.344; adjusted r^2 0.337). The variable contributing most to the model was birth weight (P<0.0005) (Table 9.12).

Since the availability of EBM (either MEBM or DEBM) at the start of feeds is also likely to affect the timing of feeds, this was considered. Although data specifically for the availability of EBM were not collected, the type of milk for the first feed was known for each baby. The use of any EBM for the first feed was considered to reflect the availability of EBM. The addition of this showed that this explained a further 6% of the variation (r^2 0.407; adjusted r^2 0.399; r^2 change 0.063). The use of any EBM then became the most highly significant contributor to the model, but all other variables remained significant.

In order to examine the effects of differences between countries, this was added to the model. This resulted in a further significant change in overall effect, suggesting that the country of hospitalization also contributes significantly to the variation in the model (r^2 0.439; adjusted r^2 0.430; r^2 change 0.032). Infants in Canadian units were fed later than those in UK units; all other effects remained significant.

9.3.4.2 Analysis by birth weight group

In order to examine more closely the effect of birth weight, further multiple regression analyses were performed for each birth weight group. Variables were entered into the regression models for each group according to the method previously defined.

(b) Birth weight <1000g (Table 9.13)

Abnormal Dopplers, the use of inotropes, indomethacin and CRIB score were significantly associated with the time to first enteral feed. The use of inotropes was the largest contributing variable and was associated with later feeding. Increasing CRIB score was related to later feeding. This model explained less than 30% of the variation (r^2 0.253; adjusted r^2 0.236). When the use of EBM was added to the model, it contributed a highly significant additional amount (r^2 0.362; adjusted r^2 0.343; r^2 change 0.109) and the effect of

abnormal Dopplers became non-significant. The addition of country did not contribute significantly to the model (r^2 0.364; adjusted r^2 0.341; r^2 change 0.002).

Table 9.12: Multivariate regression analysis to explore associations with timing of first enteral feed

Independent variable	Effect (%)	95% CI	P value
Birth weight (kg)	-1.48	-1.70, -1.28	<0.0005
Abnormal dopplers (yes/no)	1.22	1.09, 1.36	0.001
Opiate sedation days 1-3 (yes/no)	1.32	1.21, 1.44	<0.0005
Acidosis days 1-3 (yes/no)	1.24	1.10, 1.41	<0.0005
Mechanical ventilation days 1-3 (yes/no)	1.12	1.03, 1.22	0.008
Inotropic support days 1-3 (yes/no)	1.19	1.08, 1.31	<0.0005
Indomethacin days 1-3 (yes/no)	1.21	1.06, 1.39	0.005
EBM for first feed (yes/no)	1.40	1.30, 1.49	<0.0005
Country (UK/Canada)	-1.26	-1.35, -1.16	<0.0005

Table 9.13: Multivariate regression analysis to explore associations with timing of first enteral feed in babies <1000g

Independent variable	Effect (%)	95% CI	P value
Abnormal dopplers (yes/no)	1.15	1.04, 1.38	0.126
Inotropic support days 1-3 (yes/no)	1.44	1.25, 1.67	<0.0005
Indomethacin days 1-3 (yes/no)	1.35	1.11, 1.64	0.003
CRIB score	1.04	1.02, 1.06	<0.0005
EBM for first feed	1.48	1.28, 1.71	<0.0005
Country (UK/Canada)	1.05	-1.21, 1.09	0.468

(c) Birth weight 1000-1249g (Table 9.14)

IUGR, abnormal dopplers, and CRIB score were significantly associated with the time to first enteral feed. However, this model explained less than 20% of the variation (r^2 0.170; adjusted r^2 0.155). The effect of increasing CRIB score was the most highly significant factor and was associated with later feeding. Unexpectedly, IUGR was associated with earlier feeding. The effect added by the use of any EBM was significant (r^2 0.248; adjusted r^2 0.230; r^2 change 0.078) and rendered the effect of abnormal Doppler studies non-significant.

A further 4.9% of the variation was explained by the addition of country (r^2 0.297; adjusted r^2 0.275; r^2 change 0.049).

Table 9.14: Multivariate regression analysis to explore associations with timing of first enteral feed in babies 1000-1249g

Independent variable	Effect (%)	95% CI	P value
IUGR (yes/no)	-1.27	-1.49, -1.08	0.005
Abnormal dopplers (yes/no)	1.22	-1.03, 1.52	0.086
CRIB score	1.08	1.05, 1.11	<0.0005
EBM for first feed	1.43	1.24, 1.65	<0.0005
Country (UK/Canada)	-1.29	1.5, 1.11	0.001

(d) Birth weight ≥1250g (Table 9.15)

Variables significantly associated with the time of initiation of feeds in this birth weight group were IUGR, abnormal Doppler, sedation and acidosis. IUGR was unexpectedly associated with early initiation of enteral feeds. The model explained just over 25% of the variation in this group (r^2 0.267; adjusted r^2 0.254). The variable that showed the strongest relationship was opiate sedation, which was associated with later feeding. The addition of EBM to the model contributed a further 5.8% (r^2 0.325; adjusted r^2 0.310; r^2 change 0.058). The addition of EBM resulted in the effect of abnormal dopplers becoming non-significant. The addition of country to the model resulted in a statistically significant change (r^2 0.355; adjusted r^2 0.337; r^2 change 0.030).

Table 9.15: Multivariate regression analysis to explore associations with timing of first enteral feed in babies ≥1250g

Independent variable	Effect (%)	95% CI	P value
IUGR (yes/no)	-1.28	-1.44, -1.13	<0.0005
Abnormal dopplers (yes/no)	1.24	1.02, 1.57	0.067
Opiate sedation days 1-3 (yes/no)	1.54	1.32, 1.81	<0.0005
Acidosis days 1-3 (yes/no)	1.34	1.01, 1.79	0.045
EBM for first feed	1.31	1.17, 1.46	<0.0005
Country (UK/Canada)	-1.21	-1.36, -1.08	0.002

9.3.4.3 Minimal enteral nutrition

Of the 629 babies who survived to start enteral feeding, data on initial feed volumes were missing for 11 (1.7%). 584 (92.8%) received at least one day of MEN, defined as feeds of <25ml/kg/24 hours prior to attempts to increase feed volumes. 423 (67%) received minimal volumes for two or more days. Minimal nutrition volumes were started and maintained for between 1 and 16 days (median (IQR) = 2 (1, 4) days) (Table 9.16).

There was a significant difference between UK and Canadian units in the number of days of MEN given (Mann Whitney U test, P<0.001), with babies in the UK having shorter periods of MEN. In 32 (5%) infants, initial feed volumes were in excess of 25ml/kg/day and were advanced immediately. Of these infants, 31 were from UK units, compared with only one from a Canadian unit. This represents a highly significant difference between the countries (P <0.001). Analysis of the characteristics of infants who received increasing feeds from the time of feed initiation shows that they were of higher birth weight, more mature and less sick than infants who received any MEN (Table 9.18).

The majority (84.4%) of babies progressed to increasing feed volumes after the period of minimal nutrition. However, 97 (15.6%) infants had feeds discontinued for >24 hours after commencing minimal feed volumes. All those infants who had feeds temporarily discontinued were later given a further period of MEN before volumes were increased. This second period is not included in the results above for any baby. The commonest reasons overall for discontinuing feeds during minimal feeding were the presence of bilious aspirates (26 infants) and the introduction of indomethacin therapy (23 infants). Indomethacin was the commonest reason among Canadian babies and was the indication on almost half of the occasions where MEN was discontinued temporarily. In contrast, it was a much less common reason in the UK where bilious aspirates, abdominal distension or large gastric aspirates were more likely to result in feeds being discontinued. Further reasons for discontinuation of minimal feeding are detailed in table 9.17.

Table 9.16: Number of days of minimal enteral nutrition

No. of days MEN	UK (n=406)	Canada (n=212)	Total (n=618)
None	33 (8.1)	1 (0.5)	34 (5.5)
1 day	121 (29.8)	40 (18.9)	161 (26)
2 days	113 (27.8)	33 (15.6)	146 (23.6)
3 days	58 (14.3)	38 (17.9)	96 (15.5)
4 days	36 (8.9)	30 (14.1)	66 (10.7)
5 days	21 (5.2)	19 (8.9)	40 (6.5)
6 days	11 (2.7)	20 (9.4)	31 (5)
7 days	5 (1.2)	15 (7.1)	20 (3.2)
8 days	5 (1.2)	4 (1.9)	9 (1.4)
9 days	3 (0.7)	6 (2.8)	9 (1.4)
10 days	0	1 (0.5)	1 (0.2)
≥ 11 days	0	5 (2.3)	5 (0.8)

Values are presented as n (%)

Table 9.17: Reasons for discontinuation of minimal enteral nutrition

	UK (n=52/406)	Canada (n=45/212)	Total (n=97/618)
Bilious gastric aspirates	16 (30.7)	10 (22.2)	26 (2.7)
Indomethacin	2 (3.8)	21 (46.7)	23 (23.7)
Abdominal distension / possible NEC	13 (25)	2 (4.4)	15 (15.5)
Large gastric aspirates	7 (13.5)	6 (1.3)	13 (13.4)
Re-ventilation	2 (3.8)	1 (2.2)	3 (3.1)
Blood-stained aspirates	1 (1.9)	0	1 (1)
Blood transfusion	1 (1.9)	0	1 (1)
Acidosis	1 (1.9)	0	1 (1)
Deterioration in clinical condition	5 (9.6)	4 (8.9)	9 (1)
(Respiratory distress, seizures, pneumothorax, pulmonary haemorrhage, cardiac arrest, sepsis)			
Insufficient EBM	2 (3.8)	1 (2.2)	3 (3.1)
Not known	2 (3.8)	0	2 (2)

Values are presented as n (%)

Table 9.18: Characteristics of infants receiving early advancing feeds compared with those receiving MEN

	Advancing feeds n=34	MEN n=584	P value
Birth weight (g)	1335 (932.5-1462.5)	1127.5 (935-1315)	<0.001
Gestation (weeks)	31.5 (29-34)	28 (27-30)	<0.001
CRIB score	2 (2-13)	11 (2-14)	<0.001

Values are presented as median (IQR); Mann Whitney U test for comparisons

9.3.4.4 Initiation of feeds in growth restricted babies

Of the 208 growth restricted babies, six died before being fed. The median (IQR) day to starting feeds for growth-restricted babies was Day 2 (3-4), compared with Day 3 (2-4) in babies whose birth weight was appropriate for their gestational age (AGA) at birth. This difference was highly statistically significant (Mann Whitney U test, P <0.0005). Since it would be expected that growth-restricted babies would be fed later than those who were not growth-restricted, further evaluation was necessary to explain this finding. Examination by gestational age (Table 9.19) shows that most of the babies with IUGR were in the highest gestational age groups.

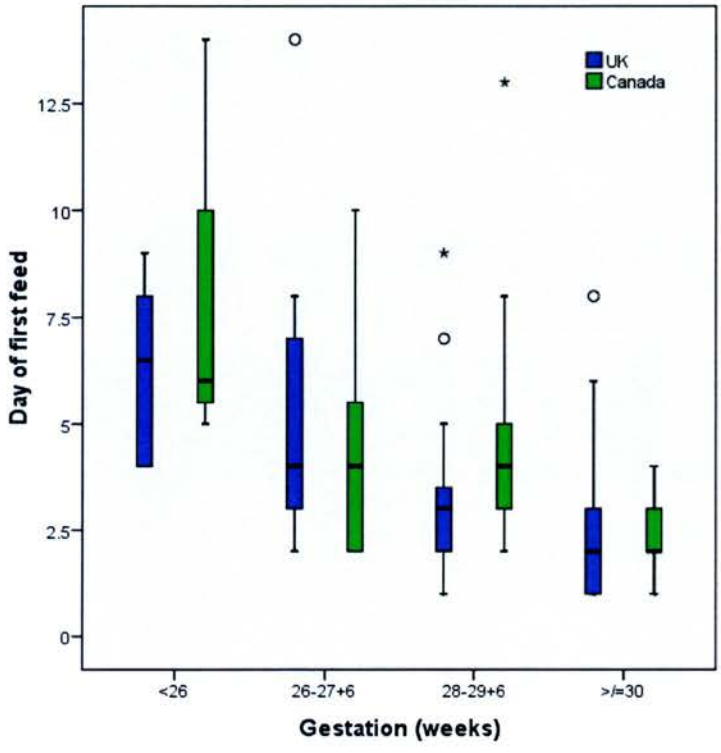
The distribution of data for the day of first feed in growth-restricted infants was highly positively skewed and was not amenable to transformation; non-parametric tests were therefore used to compare the timing of initiation of feeds between the UK and Canada. The median day for starting feeds in UK growth-restricted infants was Day 2 (2-3), compared with Day 3 (2-4) in Canadian infants, representing a statistically significant difference (P=0.026). This is illustrated in the box plot in Figure 9.6. In contrast, there was no difference between the countries for the day of starting feeds in appropriately grown infants (Median (IQR) 3 (2-4) days for both; Mann Whitney U test P=0.107).

Table 9.19: Number of IUGR babies by gestational age bands

	UK (n=451)	Canada (n=219)	Total (n=670)
<26 weeks	7 (1.5)	3 (1.4)	10 (1.5)
26-27+6 weeks	11 (2.4)	12 (5.5)	23 (3.4)
28-29+6 weeks	30 (6.6)	11 (5.0)	41 (6.1)
≥30 weeks	100 (22.2)	34 (15.5)	134 (20)
Total	148 (32.8)	60 (27.4)	208

Values are presented as n (%)

Figure 9.6: Box plot to show the day of first feed in IUGR infants by gestational age and country



*Top and bottom of boxes represent 25th and 75th percentiles; Bar represents median; Whiskers represent smallest values that are not outliers or extreme values;° represents outliers; * represents extreme values*

9.4 Advancement of feeds

Fluid volumes administered to preterm infants increase over the first few days of life, with a typical regimen starting at 60-100ml/kg/day on the first day depending on gestation and increasing by 30ml/kg/day until 150ml/kg/day. Initially, some or this entire requirement is usually given intravenously. After the introduction of enteral feeds, milk volumes are increased and intravenous volumes simultaneously decreased until the total required volume is given enterally. For the purpose of analysis, full enteral feeds were defined as 150ml/kg/day. During the first few days of life when feeds are being increased the appropriate full fluid volume is expected to be less than 150ml/kg/day. If an infant was deemed fit to receive this total required volume enterally and did not require supplementation with PN, then the infant was considered to have achieved full enteral feeding even though the volume administered may have been less than 150ml/kg/day. Twenty infants died and a further 46 infants were transferred to other centres after starting enteral feeds, but before reaching full enteral feeds. Complete paired data for the times of starting feeds and attaining full feeds were therefore available for 563 (84.2%) infants. In a further 12 cases nursing records for volumes of feed given were missing for some of the time period during which feeds were advanced. Although information was available for the time of initiation and attainment of full feeds, it was not possible to include these babies in more detailed analysis of factors affecting feed advancement. Data for the type of feed given whilst progressing to full feeds were available for 552 infants. Feeds were exclusively EBM in 352 (64%) infants. In infants of <26 weeks of gestation, 82% received only EBM and this proportion reduced to 68% in those of 26-29+6 weeks of gestation and further to 52% in infants ≥30 weeks of gestation.

Figure 9.7 shows the median feed volumes given to infants during the first 14 days of life by gestational age group. Overall, this shows that feed volumes started to increase earlier with increasing gestational age at birth and were increased more rapidly across the groups with increasing maturity. In infants of < 29 weeks of gestation, volume increases were similar between the two groups for the first week of life. Further dividing the groups according to country suggests that feeds were increased more slowly in all gestational age bands in Canadian infants than in UK born infants.

The median (IQR) day for attaining full enteral feeds was 11 (8-17 days) for the whole group. Data for the time from first to full feeds were positively skewed and were log-

transformed (Log10) for further analysis. An independent samples t test was performed to compare the time of attainment of full enteral feeds between UK and Canadian infants. There was a highly significant difference between the countries with UK infants reaching full feeds approximately 30% earlier than Canadian infants (Table 9.20).

Table 9.20: Comparison between the UK and Canada for the time of attaining full enteral feeds

	Geometric mean (95% CI)		Ratio of geometric means (95% CI)	P value
	UK (n=387)	**Canada (n=176)**		
Day of reaching full feeds	8.20 (7.74, 8.68)	12.09 (11.04,13.24)	0.68 (0.61, 0.75)	<0.0005
Time from first to full feeds (days)	10.05 (9.51,10.61)	14.50 (13.29,15.82)	0.69 (0.63, 0.76)	<0.0005

Independent samples t test; log10 transformed data

Figure 9.7: Graphs to show the median volumes of enteral feed during the first 2 weeks of life by gestational age

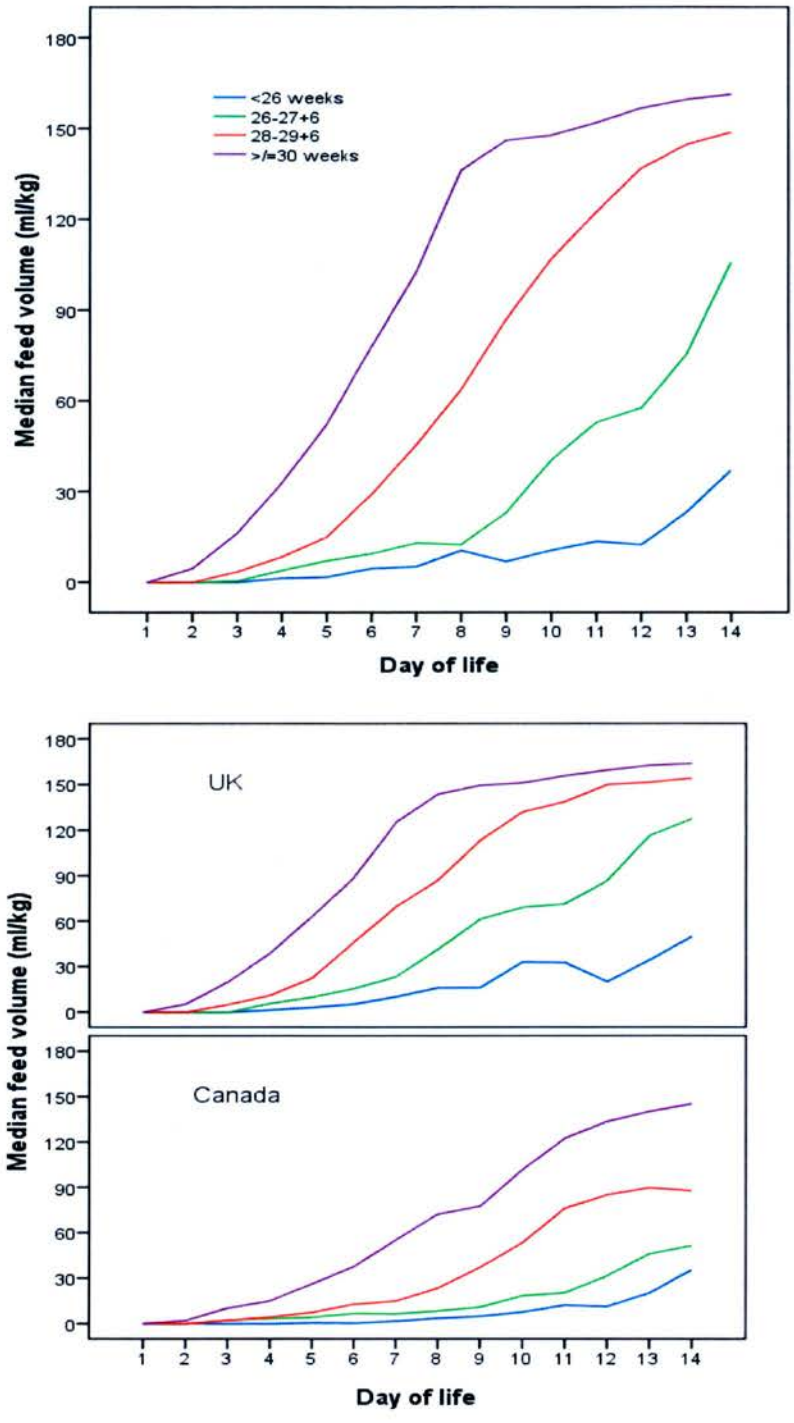
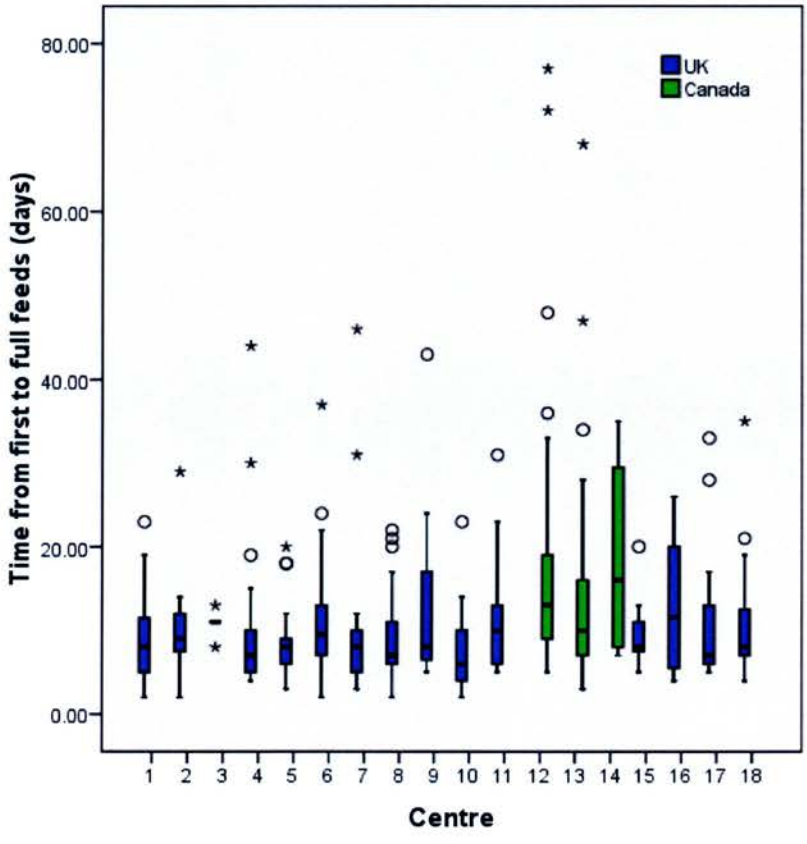


Figure 9.8 shows a box plot of the time from first to full feeds by centre. Examination of the data identifies three infants with extreme values for the length of time to attain full feeds. All

infants were from Canadian NNUs. Checking of the data showed these values to be both correct and plausible and did not identify any special characteristics about the infants that were not seen in at least some of the remaining infants. It was therefore thought that these infants might reflect true variation in practice and that exclusion would lead to the loss of valuable information. The independent samples t test was repeated after excluding these variables and showed that the differences between the countries remained highly statistically significant for the time from first to full enteral feeds (ratio of geometric means 0.70 (95%CI 0.63, 0.77; P<0.0005).

Examination of the time from first to full feeds showed that variances were unequal between centres. A Kruskal Wallis test showed a highly significant difference between the centres (χ^2 74.33; df 17; P<0.0005). Median and IQR values for each centre are shown in Table 9.21.

Figure 9.8: Box plot to show the time from first to full feeds by centre



*Top and bottom of boxes represent 25th and 75th percentiles; Bar represents median; Whiskers represent smallest values that are not outliers or extreme values;° represents outliers; * represents extreme values*

In order to identify whether differences in the time to attain full feeds existed between infants of different gestational ages or birth weight, one-way ANOVA was performed (Tables 9.22 and 9.23). There were significant differences, both for gestation and birth weight. Post hoc analysis (using the Bonferroni approach for multiple testing) showed that these differences were significant between all birth weight groups. For gestation, differences were significant between all except the two lowest gestational age groups for which the 95% confidence intervals overlapped.

Table 9.21: Median time from first to full feeds by centre

Centre	No. of infants	Median	IQR	P Value*
1	47	8	5-12	<0.0005
2	16	9	7-12	
3	5	11	9.5-12	
4	26	7	5-10	
5	47	8	6-9	
6	36	9.5	7-13	
7	20	8	5-10	
8	35	7	6-11	
9	15	8	6-19	
10	47	6	4-10	
11	9	10	5.5-18	
12	65	13	9-19	
13	103	7	10-16	
14	8	16	7.5-30.25	
15	16	8	7-11	
16	12	11.5	5.25-20	
17	17	7	5.5-14.5	
18	39	8	7-13	

**Kruskal wallis test for differences between centres*

Table 9.22: One way ANOVA for the time from first feed to full feeds by gestation

Gestation	No.	Mean time from first to full feeds*	95% CI	P Value
< 26 weeks	52	16.2	(13.91, 18.87)	<0.0005
26-27 weeks	120	13.23	(12.09, 14.48)	
28-29 weeks	198	9.30	(8.65, 10.03)	
≥ 30 weeks	193	6.33	(5.89, 6.81)	

**geometric mean*

Table 9.23: One-way ANOVA for the time from first feed to full feeds by birth weight

Birth weight	No.	Mean time from first to full feeds*	95% CI	P Value
< 1000g	174	12.68	(11.73, 13.70)	<0.0005
1000-1249g	186	9.48	(8.69, 10.35)	
>1250g	203	6.91	(6.41, 7.46)	

**geometric mean*

9.4.1 Factors influencing the rate of advancement of enteral feeds

In their responses to the survey, clinicians identified a number of factors that would lead them to progress feeds at a slower rate than usual. Some of these related to knowledge of antenatal factors and others to the baby's clinical condition and management. Table 9.19 shows the proportions of babies affected by these factors and the number of days for which they were present during the time of feed advancement. The number of days for each factor was determined by its occurrence during all or part of a 24-hour period from the day of the first enteral feed until the attainment of full feeds. Large gastric aspirates were defined as aspirated volumes of >2ml, since this was the most commonly suggested volume by clinicians in the survey. Data for the number of days of mechanical ventilation and UVC were missing for two UK babies and for sedation for one UK baby. Other factors were defined as either present or absent during the period of feed advancement. These are shown in Tables 9.24a and 9.24b. Abdominal distension was defined as any period where abdominal distension was documented by medical staff on clinical examination. Proven

sepsis was defined as a positive microbiological culture obtained from a usually sterile body fluid such as blood or cerebrospinal fluid (CSF). Positive blood cultures were identified from laboratory results, which were available for 563 babies.

Canadian infants were ventilated for significantly longer than were infants in the UK. They also had UVCs for longer and had more days on which large aspirates occurred. This analysis confirmed the higher proportions of infants diagnosed and treated for PDA in Canada compared with the UK. There were no differences between the countries for other aspects of clinical management.

Table 9.24a: Occurrence of factors potentially influencing feed advancement

	Number of babies		Number of days			
	UK (n=375)	**Canada (n=176)**	**All babies**	**UK**	**Canada**	**P value**
Ventilation	126 (33.6)	104 (59)	5 (2-13)	4 (1-9)	7 (2-19)	0.001
nCPAP	205 (54.7)	115 (65.3)	4 (2-8)	4 (2-8)	5 (2-9)	0.149
UVC	98 (26.1)	116 (66)	4 (2-6)	3 (2-4)	5 (3.25-7)	<0.0005
UAC	113 (30.1)	93 (52.8)	3 (2-4)	3 (2-4)	2 (2-4)	0.413
Sedation	78 (20.8)	23 (13)	4 (1-8.5)	5 (2-8)	3 (1-11)	0.598
Paralysis	12 (3.2)	2 (1.1)	2 (1-3.25)	2 (1-3.75)	2 (1-3)	0.791
Inotropes	28 (7.5)	12 (6.8)	2 (1-4)	2 (1-4)	2.5 (1-4)	0.965
Large aspirates	291 (77.6)	132 (75)	3 (2-6)	3 (2-6)	3 (2-4.75)	0.033
Bilious aspirates	169 (45)	90 (51.1)	2 (1-3)	2 (1-3)	2 (1-3)	0.563

Number of babies are presented as n (%); Number of days are presented as median (IQR) Mann Whitney U test for comparisons

Table 9.24b

	UK (n=375)	**Canada (n=176)**	**Total (n=551)**	**P value**
Bolus feeds (yes/no)	325 (86.7)	176 (100)	501 (90.9)	0.912
PDA (yes/no)	88 (23.4)	59 (33.5)	147 (26.7)	0.017
Indomethacin (yes/no)	58 (15.5)	68 (38.6)	126 (22.9)	<0.0005
Abdominal distension (yes/no)	100 (26.7)	43 (24.4)	143 (25.9)	0.650
Proven sepsis (yes/no)	63/387 (16.2)	28 (15.9)	91/563 (16.2)	1.0

Values are presented as n (%); χ^2 test for comparisons

9.4.1.1 Associations with the time from first feed until attainment of full feeds

(a) All infants

Complete data for the daily volumes of feed given were available for 551 surviving babies. Data were analysed using multiple regression to examine factors, including birth weight that potentially contributed to variation in the time taken to attain full enteral feeds. Variables that were potentially relevant and were present during the time from starting feeds to attaining full feeds were first analysed separately. Those which showed an association with the time from first to full feeds (log10 transformed data) on univariate analysis ($P < 0.2$) were entered into the multiple regression model. Two variables, abnormal Dopplers and bolus or continuous feeding, were not significantly associated with the time to attain full feeds. All other variables had highly significant relationships with the outcome. They were added simultaneously to the model as follows: birth weight, gestation, number of days of ventilation, CPAP, sedation, paralysis, large aspirates, bilious aspirates, UAC, UVC and inotropes, together with the presence of PDA, use of indomethacin, abdominal distension, proven sepsis, and significant events (pulmonary haemorrhage, pneumothorax or seizures). The occurrence of NEC before full enteral feed volumes were reached was also included and was divided into Stage I and Stage II/III disease.

Variables independently associated with the time to first feed were gestation, the number of days on which there were large aspirates, bilious aspirates, CPAP, mechanical ventilation, UVC and inotropes, the presence of a PDA, abdominal distension, sepsis and stage I, but not stage II/III NEC. This model accounted for 69% of the variation in the model. The variable contributing most to the model was the presence of large aspirates ($P<0.0001$).

The number of days of MEN was not included in the initial regression model. Addition of this variable resulted in explanation of a further 4.8% of the variation, but rendered the effect of inotropes and UVC non-significant (r^2 0.743; adjusted r^2 0.737; r^2 change 0.048). The addition of country to the model led to a further small change and the final model explained 75% of the variation in the time from first to full feeds (r^2 0.756; adjusted r^2 0.75; r^2 change 0.013). The effects of all other variables remained highly significant ($P<0.001$ for all; Table 9.25). Lower gestational age and either the presence of, or an increasing number of days of all significant variables was associated with longer time to attain full feeds. The inclusion of country confirmed that Canadian infants achieved full feeds later than UK infants and that this was an independent effect.

Some collinearity was detected in the model and this was explored. No two variables included in the model were highly correlated and therefore no specific variable could be identified which would be suitable for exclusion. Since the model was derived based on clinical factors believed likely to contribute to variation, it was felt inappropriate to exclude any variables arbitrarily. The factor that was responsible for collinearity was gestational age, which was related to more than one other factor. Additional analysis was therefore performed stratifying by gestational age to explore further the variation in the time to achieve full feeds. In view of the small numbers of surviving infants in the lowest gestational age band, the two lower bands were combined and analysis was performed for infants of <28 weeks, 28-29+6 weeks and ≥30 weeks of gestation

Table 9.25: Multivariate regression analysis to explore associations with the time taken to attain full enteral feeds in all babies

Independent variable	Effect (%)	95% CI	P value
Gestation (weeks)	-1.04	-1.06, -1.03	<0.0005
Large aspirates (no. days)	1.03	1.02, 1.04	<0.0005
Bilious aspirates (no. days)	1.05	1.02, 1.06	<0.0005
nCPAP (no. days)	1.01	1.00, 1.02	<0.0005
Inotropes (no. days)	-1.01	-1.04, 1.02	0.448
UVC (no. days)	1.00	-1.01, 1.01	0.616
Ventilation (no. days)	1.02	1.01, 1.02	<0.0005
Abdominal distension (yes/no)	1.17	1.09, 1.24	<0.0005
PDA (yes/no)	1.12	1.04, 1.20	0.001
NEC Stage I (yes/no)	1.30	1.16, 1.49	<0.0005
Proven sepsis (yes/no)	1.15	1.06, 1.24	<0.0005
MEN (no. days)	1.06	1.05, 1.08	<0.0005
Country (UK/Canada)	1.19	1.12, 1.28	<0.0005

(b) Infants <28 weeks of gestation

The following model explained more than 75% of the variation in the time to attain full feeds in this gestational age band: bilious aspirates, nCPAP, ventilation, IUGR and proven sepsis (r^2 0.767; adjusted r^2 0.757). The addition of the number of days of MEN exerted an effect that accounted for an additional small, but statistically significant amount of variation (r^2 0.779; adjusted r^2 0.768; r^2 change 0.012; P=0.004). Although the addition of country did not

significantly change the overall model, it rendered the effect of IUGR and MEN days non-statistically significant and substantially increased the statistical significance of the use of sedation (Table 9.26).

Table 9.26: Multivariate regression analysis to explore associations with the time taken to attain full enteral feeds in babies of <28 weeks of gestation

Independent variable	Effect (%)	95% CI	P value
Bilious aspirates (no. days)	1.02	1.00, 1.05	0.017
nCPAP (no. days)	1.03	1.02, 1.03	<0.0005
Opiate sedation (no. days)	1.01	1.00, 1.02	0.011
Ventilation (no. days)	1.03	1.02, 1.03	<0.0005
IUGR	1.13	-1.04, 1.28	0.058
Proven sepsis	1.14	1.04, 1.25	0.005
MEN (no. days)	1.02	1.00, 1.03	0.054
Country (UK/Canada)	1.11	1.00,1.23	0.053

(c) Infants 28-29+6 weeks of gestation

The exclusive use of EBM was significantly associated with earlier attainment of full enteral feeds. The presence of large gastric aspirates, bilious aspirates, respiratory support, abdominal distension, mechanical ventilation and the diagnosis of stage I NEC during the period of increasing feeds were all associated with later attainment of full feeds. This model explained more than 60% of the variation in time to full enteral feeds (r^2 0.647; adjusted r^2 0.632). Addition of the number of days of MEN to the model resulted in explanation of a further small portion of variation, and all other effects remained significant (r^2 0.682; adjusted r^2 0.666; r^2 change 0.034). The effect of adding country to the model was not statistically significant (r^2 0.683; adjusted r^2 0.666; r^2 change 0.002). The most highly significant variables in the model were large aspirates and respiratory support with nCPAP (Table 9.27)

(d) Infants ≥30 weeks of gestation

In this gestational age stratum, inclusion of exclusive feeding with EBM, large aspirates, bilious aspirates and abdominal distension resulted in a model that explained almost 50% of the variation in the time taken to reach full feeds, but in which only large or bilious aspirates and abdominal distension contributed significantly (P>0.05) (r^2 0.503; adjusted r^2 0.489; r^2

change 0.034). The addition of the number of days of MEN contributed a further 11.8% to the model (r^2 0.620; adjusted r^2 0.608; r^2 change 0.118). The subsequent addition of country increased the significance of the effect of exclusive EBM in the model and increased the significance of the overall model by almost 3%. Unexpectedly, the use of EBM was associated with later achievement of full feeds. All other variables were also related to later feeding (Table 9.28).

Table 9.27: Multivariate regression analysis to explore the associations with time taken to attain full enteral feeds in babies of 28-29 weeks of gestation

Independent variable	Effect (%)	95% CI	P value
Exclusive EBM	-1.11	-1.23, -1.01	0.036
Large aspirates (no. days)	1.03	1.02, 1.04	<0.0005
Bilious aspirates (no. days)	1.04	1.01, 1.07	0.020
nCPAP (no. days)	1.03	1.02, 1.04	<0.0005
Abdominal distension (yes/No)	1.17	1.04, 1.32	0.01
UVC (no. days)	1.02	1.00, 1.04	0.045
Ventilation (no. days)	1.02	1.01, 1.02	<0.0005
Stage I NEC (yes/no)	1.56	1.28, 1.09	<0.0005
MEN (no. days)	1.06	1.03, 1.09	<0.0005
Country (UK/Canada)	1.06	-1.06, 1.19	0.311

Table 9.28: Multivariate regression analysis to explore associations with the time taken to attain full enteral feeds in babies of ≥30 weeks of gestation

Independent variable	Effect (%)	95% CI	P value
Birth weight	-1.02	-1.31, 1.26	0.869
Exclusive EBM	1.14	1.03, 1.25	0.009
Large aspirates (no. days)	1.07	1.05, 1.08	<0.0005
Bilious aspirates (no. days)	1.08	1.02, 1.13	0.003
Abdominal distension (yes/no)	1.24	1.09, 1.32	0.01
MEN (no. days)	1.11	1.07, 1.15	<0.0005
Country (UK/Canada)	1.24	1.11, 1.38	<0.0005

9.5 Temporary discontinuation of feeds

Information about temporary discontinuation of enteral feeds was available for 557/609 surviving babies. Of these, 183 (32.8%) progressed from first to full feeds without any periods during which feeds were withheld. The remaining 374 babies had feeds discontinued for one or more hours. Table 9.29 shows that the largest proportion of babies had feeds discontinued for less than 6 hours. However, more than a quarter had feeds withheld for a period equivalent to three to seven days in total. In a small number of babies, feeds were withheld for a total number of hours that was equivalent to two or three weeks.

Table 9.29: Number of hours of discontinued feeds

Number of hours	Number (%) of babies		
	UK	**Canada**	**Total**
	n (%)	**n (%)**	**n (%)**
0	130 (34.2)	53 (29.9)	183 (32.8)
1-6	60 (15.8)	18 (10.2)	78 (11.6)
7-12	32 (8.4)	10 (5.6)	42 (6.3)
13-24	41 (10.8)	17 (9.6)	58 (8.7)
25-48	36 (9.5)	20 (11.3)	56 (8.4)
49-72	21 (5.5)	18 (10.2)	39 (5.8)
73-168	40 (10.5)	26 (14.7)	66 (9.9)
169-240	11 (2.9)	5 (2.8)	16 (2.4)
241-336	8 (2.1)	2 (1.1)	10 (1.5)
337-504	1 (0.3)	5 2.8)	6 (0.9)
>505	0	3 (1.7)	3 (0.5)
Total	**380**	**177**	**557**

Table 9.30 details the reasons why feeds were discontinued for part or all of a 24-hour period during advancement to full feeds and the number of babies for whom feeds were omitted. The table includes a number of the factors highlighted by clinicians in the survey as reasons for slowing or discontinuing enteral feeds. The most frequently documented reason for discontinuation of feeds was the presence of large gastric aspirates and this affected 37% of the babies. Other factors indicative of possible intra-abdominal pathology were common

reasons. Other non-specific indicators of clinical deterioration, sepsis, the need for intubation, apnoea and respiratory distress also prompted discontinuation of feeds. A number of babies had feeds omitted during blood transfusions, indomethacin treatment or procedures or because of lack of availability of EBM. Other less commonly documented reasons were PDA, large air aspirates, gastro-oesophageal reflux, loose stools, hypoglycaemia, seizures, acidosis, surgery and fluid restriction, which each affected less than five babies. On 115 occasions in 46 babies, feeds were omitted for up to 24 hours, but no reason could be determined from the medical or nursing records.

Analysis was performed using non-parametric tests to compare the numbers of hours for which feeds were withheld according to the presence or absence of potentially influential factors during the time from first feed to attaining full feeds. Infants who were treated for Stage II or III NEC before reaching full feed volumes were excluded from the analysis, as withholding of feeds is part of therapy for the disease. This showed that treatment with indomethacin, sepsis or other significant event, the need for ventilation, nCPAP or inotropes, opiate sedation and the presence of umbilical catheters during this period were all highly significantly associated with an increase in feed discontinuation (Table 9.31). Infants who received exclusively breast milk feeds also had feeds discontinued for more hours.

In infants who had attained full feeds, feeds were discontinued in smaller proportions of babies, but for similar reasons. However, feeds were withheld in a larger proportion of babies for vomiting (6.6%), and during blood transfusion (4.3%). Indomethacin was more frequently associated with stopping feeds in Canada than in the UK before and after full feeds were established. Withholding of feeds during transfusion, either before or after infants had attained full feeds, was confined to four neonatal units in the UK. Figure 9.9 shows the variation in time for which feeds were withheld between neonatal units. Analysis using a Kruskal Wallis test showed that this variation was significant (P=0.011).

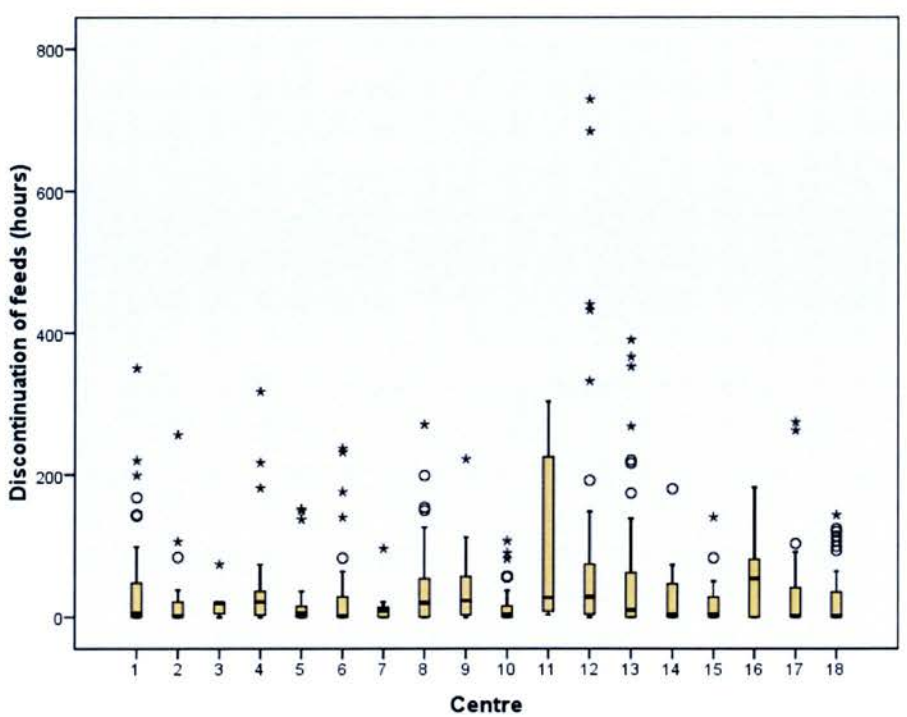
Table 9.30: Reasons for temporary discontinuation during feed advancement

	UK (n=380)		Canada (n=177)		Total (n=557)	
	No. days	No. (%) babies	No. days	No. (%) babies	No. days	No. (%) Babies
Large gastric aspirates	274	141 (37)	146	67 (37.8)	420	208 (37.3)
Bilious gastric aspirates	112	63 (16.6)	122	46 (26)	234	109 (19.5)
Abdominal distension	125	40 (10.5)	28	16 (9)	153	56 (10)
Suspected NEC	50	10 (2.6)	56	5 (2.8)	106	15 (2.7)
Proven NEC	14	2 (0.5)	52	2 (1.1)	66	4 (0.7)
Suspected NEC	50	10 (2.6)	56	5 (2.8)	106	15 (2.7)
Blood-stained aspirates	12	9 (2.4)	2	2 (1.1)	14	11 (2)
Vomiting	45	29 (7.6)	10	6 (3.4)	55	34 (6.1)
No EBM	48	31 (8.1)	1	1 (0.6)	49	32 (5.7)
Suspected/ proven sepsis	16	6 (1.6)	42	12 (6.8)	58	18 (3.1)
Respiratory distress	27	11 (2.9)	14	5 (2.8)	41	16 (2.9)
Clinical deterioration	69	29 (7.6)	18	11 (6.2)	87	40 (7.2)
Intubation	28	23 (6)	23	18 (10.2)	51	41 (7.4)
Recent extubation	25	20 (5.2)	9	9 (5.1)	34	29 (5.2)
Apnoea/ bradycardia	17	14 (3.6)	10	5 (2.8)	27	19 (3.4)
Indomethacin	26	11 (2.9)	91	31 (17.5)	117	42 (7.5)
Clinical procedure	13	10 (2.6)	17	16 (9)	30	26 (4.7)
Blood transfusion	17	11 (2.9)	0	0	17	11 (2)
Reason not identified	78	35 (9.2)	37	11 (6.2)	115	46 (8.2)

Table 9.31: Comparison of the total number of hours for which feeds were withheld according to the presence of potentially influencing factors

	Number of hours of feeds withheld		Significance (P value)
Factor present	**No**	**Yes**	
Indomethacin	3 (0-25)	52.5 (12.5-109)	<0.000005
Significant event	8 (0-44)	73.5 (20-111)	<0.0005
Sepsis	4 (0-28)	79.5 (25.5-146.5)	<0.000005
nCPAP	0 (0-19)	18 (3-64)	<0.000005
Ventilation	2 (0-17)	30 (8-93)	<0.000005
Inotropes	7.5 (0-42)	34 (7-105)	<0.0003
Abdominal distension	3 (0-22)	58 (18-121)	<0.000005
UVC	1 (0.15.5)	26 (5-74)	<0.000005
UAC	2 (0-21)	24 (4-71.5)	<0.000005
Opiate sedation	5 (0-30)	55 (8.5-143.5)	<0.000005
Bolus feeding	3 (0-29)	8 (0-48)	0.150
Exclusive EBM	3 (0-35)	12.5 (0-56.5)	<0.0005

Figure 9.9: Boxplot to show the variation in length of time for which feeds were withheld in babies in different centres



*Top and bottom of boxes represent 25th and 75th percentiles; Bar represents median; Whiskers represent smallest values that are not outliers or extreme values;° represents outliers; * represents extreme values*

9.6 Maintenance of enteral feeding

Data were collected for each infant from the time of initiation of enteral feeding until two weeks after attaining full feeds, or until the time of discharge or transfer, if this occurred earlier. During this time, the majority of infants received a combination of different types of enteral feed. Although 577 (86%) infants were given some expressed breast milk (either maternal or donated), only 156 (23.3%) were exclusively fed using EBM. A further 95 (14.2%) infants received mostly EBM. In these infants, breast milk feeds in the first few days of life were supplemented with formula milk only until the supply of EBM was adequate for all feeds.

One hundred and eighty-one (27%) infants received EBM initially, but then changed to a formula. In 144 babies, this was preterm formula and in 10 cases term formula; 27 infants were first changed from EBM to term formula before finally being given preterm formula. In a further 27 (4%) infants, the transition from EBM to preterm or term formula was bridged by the use of hydrolysed protein formula. Other infants who received some EBM were fed using a combination of milks from the time of feed initiation. The commonest was mixed feeding with EBM and preterm formula (n=100 (14.9%)). Hydrolysed formula was used to supplement feeding with EBM in 17 (2.5%) infants.

The remaining infants did not receive any EBM. Thirty-one (4.6%) infants were fed using preterm formula alone, 3 (0.4%) using term formula alone and nine (1.3%) using a combination of the two. Hydrolysed protein formula was used together with term or preterm formula in six (0.8%) infants. Forty-two (6.3%) infants did not receive any enteral feed during the study period, because of death or early transfer to another hospital; data were unavailable for the type of feeds in two (0.3%) infants.

9.6.1 Factors influencing type of milk used for maintenance of enteral feeding

9.6.1.1 Birth weight and gestational age

Figure 9.10 shows the type of feed given to infants in different birth weight categories. The proportions of babies receiving exclusive or early breast milk were highest in the lowest birth weight group. The proportion of infants receiving mixed feeding rose with increasing birth weight to approximately twice that of the smallest group. As might be expected, the

proportion of exclusively formula fed infants was highest in the larger infants and in this group was 1.5 to 2.0 times higher than in the smaller infants. A chi-square test showed a significant association between birth weight and type of milk feeds given (χ^2 =34.19; P<0.0005). However, no significant association was found between IUGR and type of feed given (χ^2 =3.87; P=0.424)

Figure 9.10: Bar chart to show types of milk fed to infants by birth weight

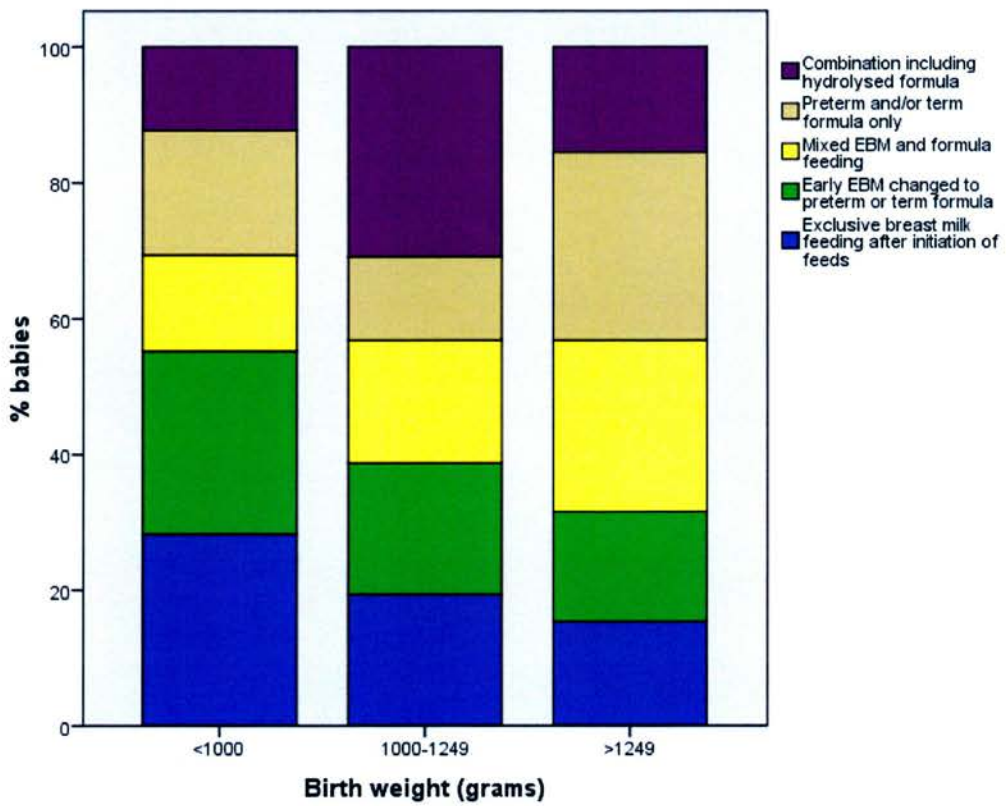
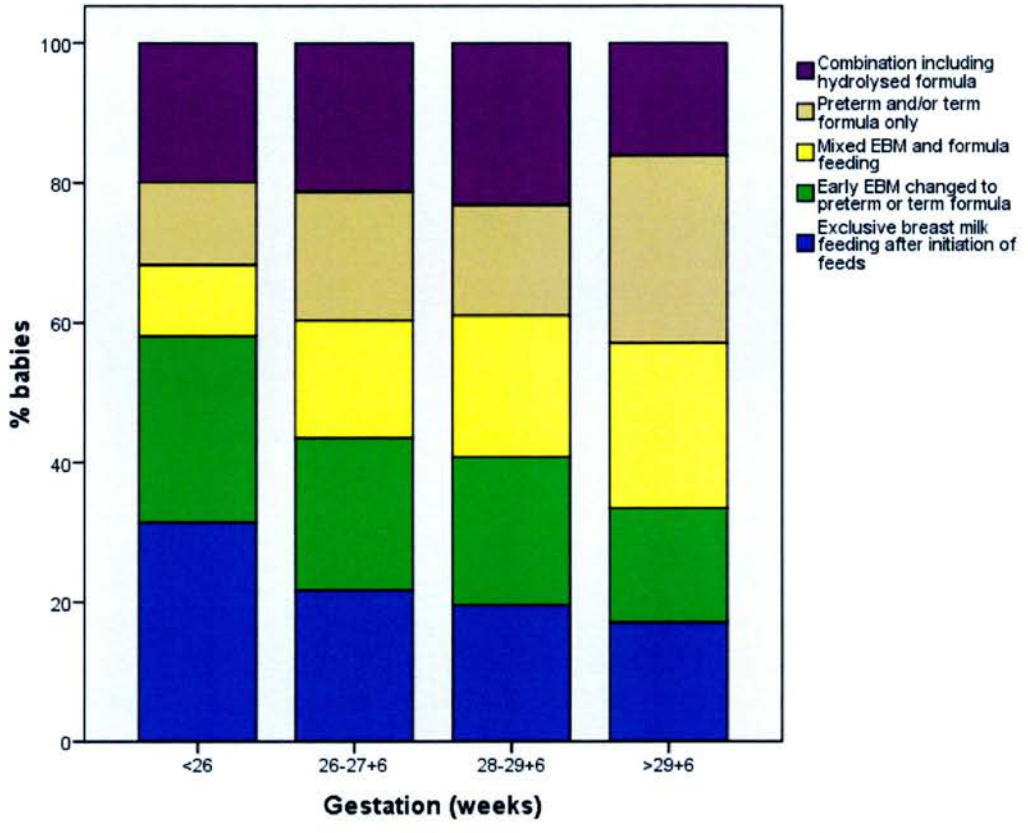


Figure 9.11 shows the types of milk fed to infants by gestational age band. This shows similar trends to those seen in the birth weight groups, but the association between gestation and type of feed fails to reach statistical significance (χ^2 =16.255; P=0.180). Hydrolysed formula was used in 15-20% of infants in each gestational age band.

Figure 9.11: Bar chart to show types of milk fed to infants by gestation at birth



9.6.2 Variation in clinical practice between centres

Figure 9.12 shows the types of milk fed to infants in each neonatal unit. Although numbers of babies for each unit were small, there appeared to be differences in practice between units and countries. There was wide variation in the proportions of babies established on exclusive breast milk feeds, ranging from 0% to approximately 70%. The use of hydrolysed formula varied, with three units using it in a large proportion of babies, compared with much smaller proportions in other units; in some units, no babies received hydrolysed formula. The use of early preterm or term formula was lowest in units where the use of either EBM or hydrolysed formula was greatest. However, in units where a high proportion of babies received hydrolysed formula, only small numbers of infants received EBM, suggesting that hydrolysed formula may have been used in place of EBM where mothers were unable, or chose not to express breast milk.

Figures 9.12, 9.13 and 9.14 show that the pattern of feeding, in this group of infants was different between the two countries. Early breast milk feeding with subsequent change to formula feeding appeared to be common in units in the UK. In contrast, in Canadian units (Units 12, 13, 14), mixed feeding from the outset appeared to be more the norm. A greater proportion of UK babies received early feeding with EBM, but a larger proportion of Canadian infants received all or some breast milk during the total time observed. The proportion of babies established on exclusive breast milk feeds was larger in the Canadian group.

Figure 9.12: Bar chart to show types of milk fed to infants in each neonatal unit

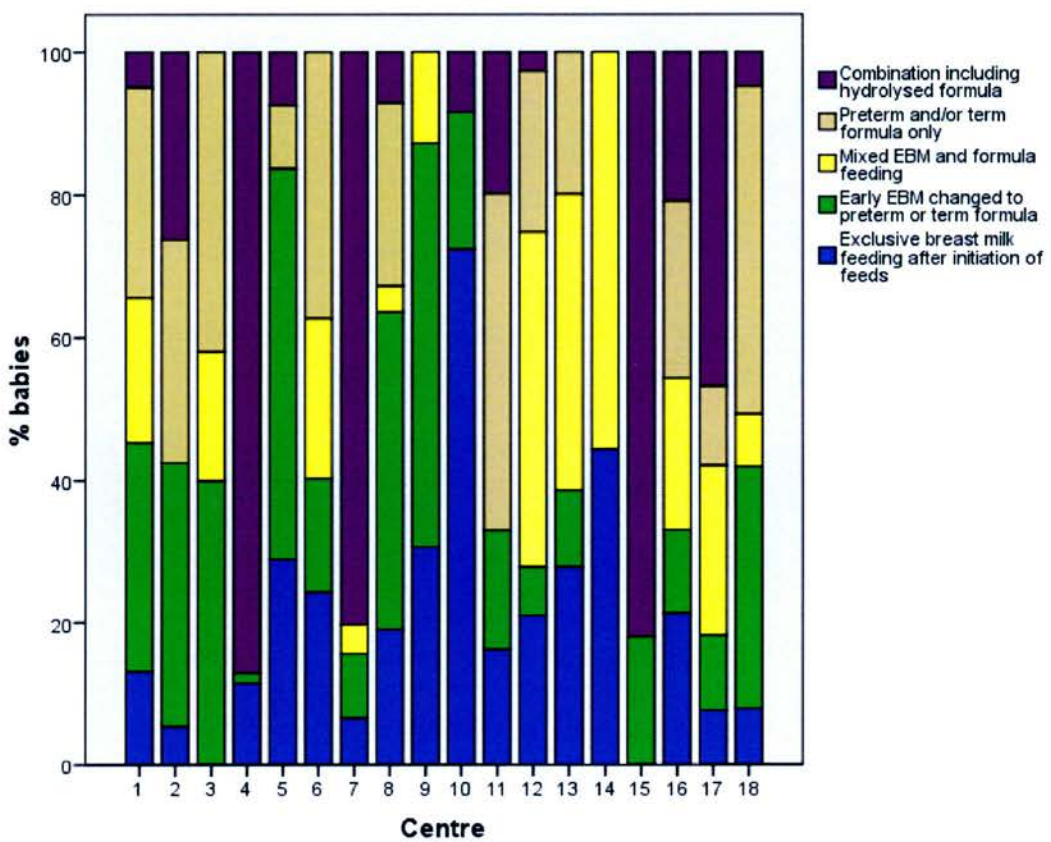


Figure 9.13: Bar chart to show type of feed given by country

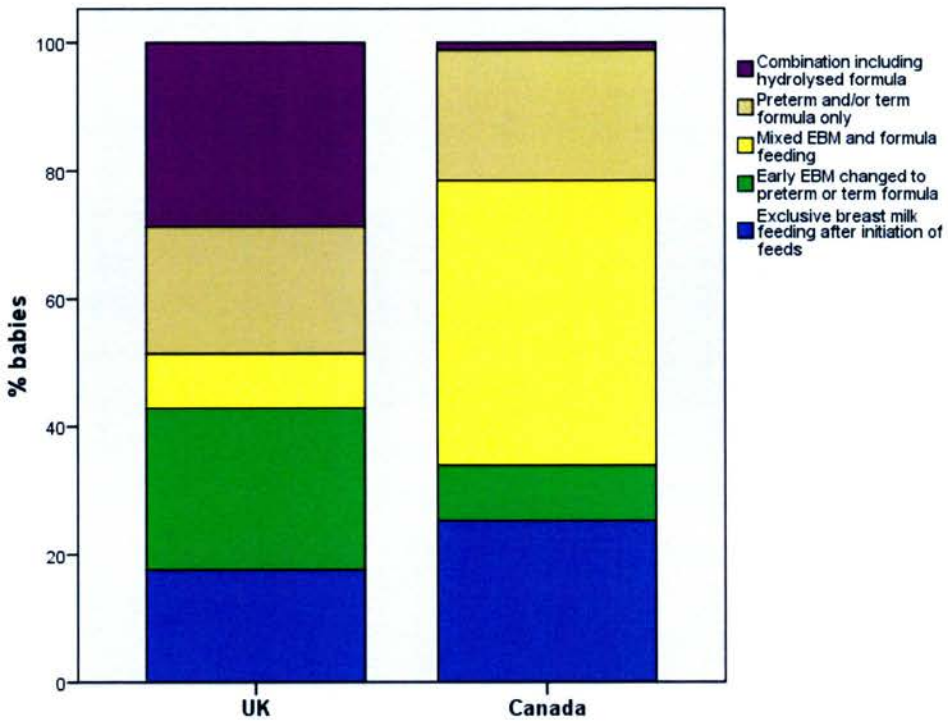
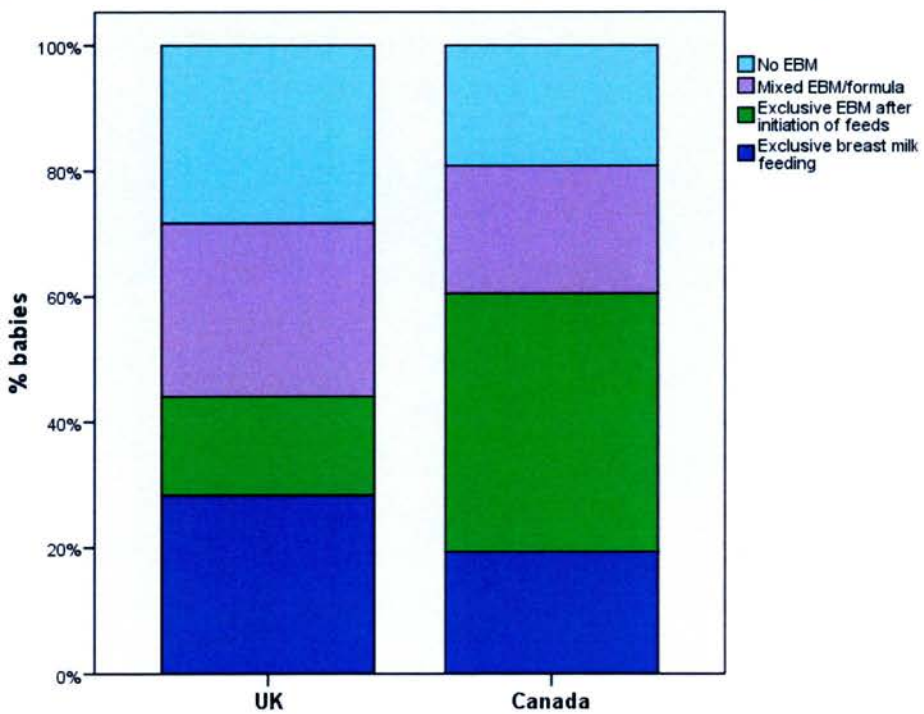


Figure 9.14: bar chart to show percentage of babies receiving EBM by country



9.7 Use of breast milk fortifier

Human milk fortifier was added to feeds for 175/518 (33.8%) infants who survived to reach full enteral feeds and received any EBM. Of those infants who were exclusively fed on breast milk once feeding was established, 93/228 (42%) received HMF. There was wide variation in practice between units, with some adding HMF to all those receiving exclusive breast milk feeds and other units not using it at all. Comparison with Figure 9.12 suggests that in some cases, units not using HMF were those where large proportions of babies changed from EBM to preterm formula feeding rather than continuing exclusive breast-feeding.

Table 9.32: Number of babies receiving HMF

Centre (no. surviving to full feeds)	**Any EBM** n (%)	**HMF** n (% of those receiving any EBM)	**Exclusive EBM** n (%)	**HMF** n (% of those receiving exclusive EBM)
1 (n=47)	42 (89)	4 (9.5)	10 (21)	1 (10)
2 (n=16)	14 (87.5)	0	2 (12.5)	0
3 (n=5)	4 (80)	3 (75)	0	0
4 (n=26)	23 (88.5)	12 (52)	8 (31)	7 (67)
5 (n=47)	46 (98)	0	19 (40)	0
6 (n=36)	31 (86)	5 (16)	17 (47)	4 (23.5)
7 (n=20)	18 (90)	14 (78)	5 (25)	5 (100)
8 (n=35)	32 (91)	25 (78)	8 (23)	8 (100)
9 (n=15)	15 (100)	5 (33)	7 (47)	4 (57)
10 (n=48)	48 (100)	0	39 (81)	0
11 (n=9)	7 (78)	1 (14.3)	4 (44)	1 (25)
12 (n=65)	59 (91)	29 (49)	30 (46)	17 (57)
13 (n=103)	98 (95)	47 (48)	55 (53)	31 (56)
14 (n=8)	8 (100)	7 (87.5)	5 (62.5)	5 (100)
15 (n=16)	13 (81)	1 (7.7)	1 (6.2)	0
16 (n=12)	10 (83)	3 (30)	5 (42)	3 (60)
17 (n=17)	16 (94)	4 (25)	6 (37.5)	2 (33)
18 (n=39)	34 (87)	15 (44)	7 (18)	7 (100)
Total (n=564)	**518 (90)**	**175 (34)**	**228 (40)**	**95 (42)**

9.8 Management of gastro-oesophageal reflux

Every type of medication commonly prescribed in the management of gastro-oesophageal reflux was used in this group of babies (Table 9.33). The use of feed thickeners and Gaviscon were confined to the UK and metoclopramide was only given in Canadian units. H_2 receptor antagonists and domperidone were used in both countries. Overall, up to 10% of babies received some form of pharmacological treatment.

Whilst the use of alginates, feed thickeners and prokinetics are generally confined to the management of gut dysmotility or reflux, H_2 receptor antagonists are also used in the prevention or treatment of gastro-intestinal bleeding associated with the use of drugs known to cause gastro-intestinal irritation, such as steroids. A total of 46 babies received steroids during the period of the study and of these, 13 also received H_2 receptor antagonists. It is therefore not possible to be certain of the indication for treatment in these cases.

Table 9.33: Numbers of babies treated with anti-reflux therapies

	UK (n=451)	Canada (n=219)	Total (n=670)
Feed thickener	**12 (2.7)**	**0**	**12 (1.8)**
Gaviscon	**63 (14.0)**	**0**	**63 (9.4)**
H_2 receptor antagonists	**53 (11.7)**	**15 (6.8)**	**68 (10.1)**
Domperidone	**15 (3.3)**	**10 (4.5)**	**25 (3.7)**
Metoclopromide	**0**	**7 (3.2)**	**7 (1.0)**
Proton pump inhibitors	**1 (0.2)**	**0**	**1 (0.1)**

Values are presented as n (%)

9.9 Necrotising enterocolitis

Proven NEC was defined according to criteria for Bell Stage II or III disease in cases where reports of radiological investigations were available. Where the diagnosis was based on clinical features such as abdominal distension, tenderness or bloody stool, infants were included if the medical records specifically documented on multiple occasions that a diagnosis of NEC had been made, even if the report of an x-ray was not available. Although most infants with a clinical or radiological diagnosis of NEC were treated with triple

antibiotic therapy for more than one week, this was not universal. However, it was regarded as supporting evidence of a firm diagnosis.

Since NEC is extremely rare in the first few days of life before enteral feeds are started, it is appropriate to compare the group who developed the disease with those surviving until a time at which they might reasonably be considered to be at risk of NEC. Infants dying during the first five days of life (n=35) were therefore not included in the following data analysis. Two of these excluded infants had received enteral feeds totaling <2ml/kg on day 3 or 4 of life.

9.9.1 Characteristics of Infants with Stage II/III NEC

Of the 635 infants surviving more than five days, 28 babies (4.4%) from twelve neonatal units developed proven NEC. The proportions of babies developing NEC were similar in the UK (17/421 (4.2%)) and Canada (11/214 (5.4%)) (χ^2 0.409; P=0.523). Of these, 12 (43%) had stage II and 16 (57%) had stage III disease. These infants were of lower gestational age and birth weight than those who did not develop NEC (Table 9.34). There was significantly more growth restriction among infants with NEC although numbers were very small and this was not accompanied by a difference in the number of infants with abnormal antenatal Doppler studies. Infants developing NEC required umbilical catheters for significantly longer than infants that did not go on to develop the disease. Other potentially relevant factors were not significantly different between the two groups.

Table 9.35 shows results of a binary logistic regression analysis. Data were missing for the day of first feed for eight babies, presence of UVC and UAC for 7 and 6 babies respectively. CRIB score was unavailable for 51 babies and the time to reach full feeds was missing for 8 babies who died and 45 who were transferred before reaching full feeds. In order to include those infants who died from NEC before reaching full enteral feed volumes, the time to either full feeds or death was included in the model. Complete data for 532/635 babies were available for this analysis, of whom 25 were infants that developed NEC. The remaining 3 infants with NEC, but for whom data were not complete, were excluded. This analysis shows that infants of lower gestation and those who had a shorter period of MEN had increased odds of developing NEC; those who took longer to reach full feeds and those who received indomethacin had decreased odds.

The proportion of babies developing NEC was highest (15.1%) in infants born at <26 weeks band and fell with increasing gestational age (Table 9.36). Stage III NEC was confined to infants of less than 30 weeks of gestation at birth. Although a greater percentage of babies with NEC weighed <1000g at birth, both Stage II and Stage III disease were seen in babies in the two larger birth weight groups in similar proportions(Table 9.37). Although univariate analysis comparing infants developing stage II and stage III NEC (Table 9.38) showed that infants with stage III NEC progressed from first to full feeds faster than those with stage II disease, multivariate analysis showed no significant associations in this small group of babies.

Table 9.34: Univariate analysis of characteristics of infants with and without proven NEC

	No NEC (n=607)	NEC Stage II/III (n=28)	P value
Gestation (weeks)	29 (27-30)	27 (24.25-28)	<0.0005
Birth weight (g)	1145 (950-1330)	955 (677-1260)	0.004
CRIB score	1 (1-4)	2 (1-7.25)	0.042
Day of first feed	3 (2-4)	4 (2-5)	0.022
Time from first to full feeds (days)	9 (6-13)	12 (7-20.25)	0.014
Exclusive EBM	237 (39)	14 (50)	0.155
MEN (days)	2 (1-4)	2 (1-4)	0.774
IUGR	199 (32.8)	3 (10.7)	0.025
Abnormal dopplers	70 (11.5)	3 (10.7)	1.00
PDA	143 (23.6)	7 (25.0)	1.00
Indomethacin	138 (22.7)	6 (21.4)	0.872
UVC (days)	0 (0-5)	4.5 (0-7)	0.032
UAC (days)	0 (0-4)	4 (0-8)	0.001
Deaths	66/642 (10.3)	9/28 (32.1)	<0.0005

Values for continuous variables are presented as median (interquartile range);

Values for categorical variables are presented as n (%).

Mann Whitney U test for continuous variables; χ^2 or Fisher's exact test for categorical variables

Table 9.35: Logistic regression analysis showing characteristics of infants and predictors for developing Stage II/III NEC

	Effect	Odds ratio (OR)	95% CI for OR	P value
Gestation (weeks)	-0.35	0.70	0.51, 0.97	0.033
CRIB score	0.08	1.08	0.89, 1.32	0.432
Day of first feed	-0.08	0.92	0.70, 1.21	0.551
Time from first to full feeds or death (days)	0.05	1.051	1.01, 1.10	0.020
Exclusive EBM	0.23	1.26	0.49, 3.27	0.635
MEN (days)	-0.23	0.48	0.64, 0.10	0.048
IUGR	-0.87	0.42	0.10, 1.72	0.227
PDA	-0.36	0.96	0.26, 3.58	0.957
Indomethacin	-1.70	0.183	0.04, 0.83	0.028
UVC (days)	0.01	1.01	0.88, 1.14	0.927
UAC (days)	0.04	1.04	0.90, 1.21	0.552
H_2 receptor antagonists	-0.38	0.68	0.18, 2.52	0.567

Table 9.36: Distribution of Stage II and III NEC by gestation at birth

Gestation (weeks)	<26 (n=66)	26-27+6 (n=132)	28-29+6 (n=226)	≥ 30 (n=211)	All (n=635)
No proven NEC	56 (84.8)	125 (94.5)	218 (96.5)	208 (98.5)	607 (95.7)
Stage II	3 (4.5)	5 (4)	1 (0.4)	3 (1.5)	12 (18.9)
Stage III	7 (10.6)	2 (1.5)	7 (3.1)	0	16 (2.5)
Total proven NEC	10 (15.1)	7 (5.6)	8 (3.7)	3 (1.4)	28 (4.4)

Values are presented as n (%).

Table 9.37: Distribution of Stage II and III NEC by birth weight

Birth weight (g)	< 1000 (n=196)	1000-1249 (n=210)	≥1250 (n=229)	All (n=635)
No proven NEC	181 (92.3)	204 (97)	222 (97)	607 (95.7)
Stage II	7 (3.5)	2 (1)	3 (1.3)	12 (18.9)
Stage III	8 (4.1)	4 (2)	4 (1.7)	16 (2.5)
Total proven NEC	15 (7.6)	6 (2.8)	7 (3.0)	27 (4.4)

Values are presented as n (%).

Table 9.38: Univariate analysis of characteristics of infants with Stage II and Stage III NEC

	NEC Stage II (n=12)	NEC Stage III (n=16)	P value
Gestation (weeks)	27 (25.25-29.5)	27 (24-28)	0.423
Birth weight (g)	952.50 (760-1257.50)	952.50 (666.5-1240)	0.763
CRIB score	2 (1-4.25)	3.5 (1-10)	0.503
Day of first feed	4 (3-4.5)	3.5(2-5.75)	0.778
Time from first to full feeds (days)	18 (12-21.75)	7 (6.75-14)	0.026
Exclusive EBM	5 (41.6)	9 (56.2)	0.146
MEN (no. days)	2 (1-4)	2 (1-4)	0.838
IUGR	2 (16.7)	1 (6.2)	0.389
Abnormal dopplers	2 (16.7)	1 (6.2)	0.389
PDA	3 (25)	4 (25)	0.666
UVC (no. days)	6 (0.5-7)	4 (0-5.5)	0.799
UAC (no.days)	4 (0-7.5)	4 (0.5-8)	0.422
Day of diagnosis of NEC	27 (12.25-42.25)	16 (11.25-21.75)	0.121

Values for continuous variables are presented as median (interquartile range); Values for categorical variables are presented as n (%).Mann Whitney U test for continuous variables; χ^2 or Fisher's exact test for categorical variables

9.9.2 Deaths due to NEC

Nine infants (26%) with a diagnosis of proven NEC died, all of whom had stage III disease. Causes of death were not always recorded in the medical notes and death certificates were not available. Death due to NEC was therefore defined as death whilst undergoing medical or surgical treatment for NEC in the presence of ongoing signs of the disease. Eight of the nine deaths were attributable to NEC. Three deaths were in UK infants and five in Canadian infants (17.6% and 45% of those with the disease respectively). Although a greater proportion of babies died of NEC in Canadian neonatal units, the overall difference in deaths due to NEC was not statistically significant between the countries (χ^2 0.2.994; Fisher's exact test P=0.091). Deaths occurred in all birth weight groups, but were confined to infants of <30 weeks of gestation. Numbers of deaths from NEC according to gestational age at birth were 4/10 (40%), 2/7 (28.6%), 2/8 (25%) respectively for babies <26 weeks, 27-28+6 weeks and 29-30+6 weeks respectively.

9.9.3 Enteral feeds in babies developing NEC

9.9.3.1 Type of feed

All had received some enteral feed prior to developing the disease. Data for the type of feed given were available for 27/28 infants developing Stage II or III NEC. All except one had received some EBM and 14/28 were exclusively breast fed after establishing early feeding and up until the time of diagnosis of NEC. Table 9.39 shows the range and combination of feeds given to babies that then developed NEC.

Table 9.39: Feeds given to babies before diagnosis of NEC

Type of feed	Stage II NEC	Stage III NEC	Total
Exclusive MEBM	5	8	13
Exclusive MEBM/DEBM		1	1
MEBM, then change to PTF		2	2
MEBM with TF, then change to PTF		2	2
MEBM with HF, then change to PTF	1		1
MEBM then Mixed MEBM/PTF	2	1	3
Mixed MEBM/PTF	1	2	3
MEBM then change to TF	1		1
PTF	1		1
Missing	1		1
Total	**12**	**16**	**28**

PTF: preterm formula; TF: term formula; HF: hydrolysed protein formula

9.9.3.2 Initiation and advancement of feeds

Infants with NEC started feeds later and took longer to reach full feeds than those without NEC (Table 9.29). There was no difference in the number of days of MEN between those with and without NEC or between those with Stage II and Stage III NEC. However, infants with Stage III NEC attained full feed volumes more rapidly than those with Stage II disease. Figure 9.15 shows a graph of the volumes of enteral feed given during the first two weeks of life to babies with and without proven NEC and indicates that during the first week, those developing stage III disease were fed at approximately the same rate as those that did not

develop NEC. However, infants with Stage II disease had a slower rate of increase. Figure 9.16 shows that this was the case regardless of gestational age, but that in infants of 29-30+6 weeks of gestation, those with either stage II or III disease were fed more rapidly than those that did not develop NEC.

Figure 9.15: Graph to show median feed volumes in infants with and without NEC

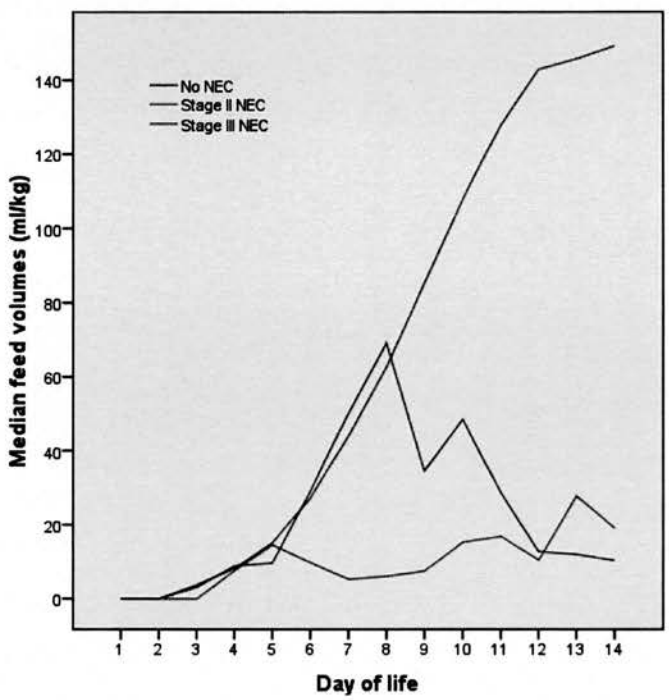
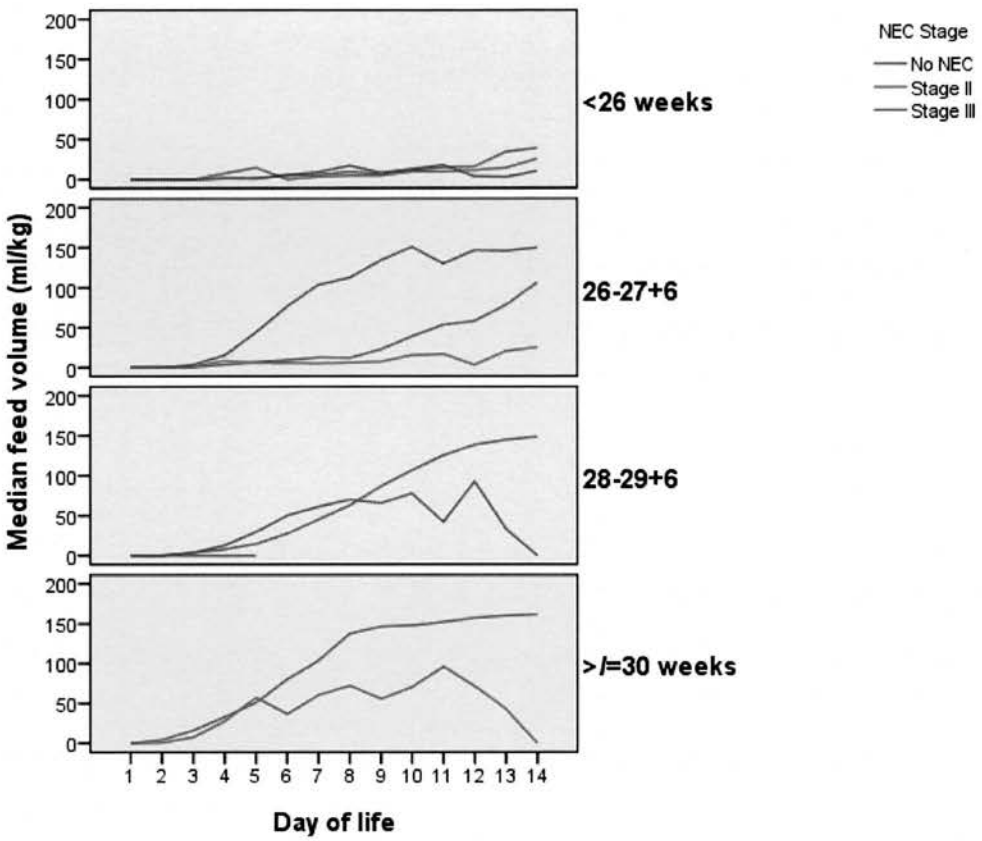


Figure 9.16: Graph to show median feed volumes in infants with and without NEC by gestational age band



The number of babies with NEC was too small to be able to analyse less common characteristics. The characteristics of each baby and presence of factors that might influence the risk of NEC are therefore described in detail in Tables 9.40-9.42. Table 9.40 shows demographic data, factors present before birth and in the early days of life. Table 9.41 describes feed-related factors and Table 9.42 describes other factors that have less commonly been associated with NEC in some studies. Eight infants required surgery for NEC and in these infants. All of these infants had radiological signs of NEC prior to surgery and the diagnosis was confirmed by histopathological findings at operation. In sixteen infants the diagnosis was made in the light of radiological evidence of pneumotosis intestinalis and in three infants with stage II disease, x-ray reports were not available, but the diagnosis was evident from medical records, length of treatment with antibiotics and withholding of feeds. One infant was transferred to another hospital before the diagnosis was made, but post mortem findings were documented. The day of diagnosis of NEC varied considerably between babies. Eight infants, four of whom died, developed the disease before

full feeds had been established and the others had spent varying amounts of time on full feed volumes. Infants who died from NEC did so within 72 hours of the diagnosis being made in all cases. Only one infant died later and this was attributable to sepsis rather than bowel disease.

Only three infants received blood transfusions within 72 hours of a diagnosis of NEC. Two of these had been established on full feeds for ≥10 days and the other had recently achieved full feeds. Data for haemoglobin levels at the time of transfusion were not collected. Seven infants had received H_2 receptor antagonists before developing NEC, but only one within 72 hours of the diagnosis. Only four infants were receiving HMF at the time of developing NEC and all had stage II disease. In four babies, the development of NEC was temporally related to reaching full feeds, occurring within 48 hours. Six babies changed from receiving EBM to either preterm or term formula after reaching full feeds, but in only one was this temporally related to the diagnosis of NEC.

There were five infants for whom a significant potentially hypoxic event occurred before the diagnosis of NEC was made and a further one infant who had had surgical intervention for spontaneous intestinal perforation before later developing NEC. Of the infants who may have suffered a hypoxic event, three were within the first 3 days of life and infants developed NEC before two weeks of age. One case of late NEC appeared to follow on within a very short time (less than 24 hours) of an episode of cardiac arrest (Table 9.42).

	Country	Gestation (weeks)	Birth weight (g)	Sex	CRIB score	IUGR (<10th centile)	Documented abnormal Dopplers	PDA	Indomethacin	UVC/UAC (days)	Diagnosis	Stage of NEC	Day of NEC	Day of Death	Death due to NEC
1	**UK**	24	635	M	3	No	No	No	No	8	Surgical	III	8	No	
2	**UK**	24	530	M	10	Yes	No	Yes	No	16	Surgical	III	68	No	
3	**UK**	24	590	M	10	No	No	No	No	8	Radiological	III	12	13	Yes
4	**Can**	24	720	M	11	No	No	Yes	Yes	18	Radiological	III	6	No	
5	**Can**	24	663	M	8	No	No	No	Yes	0/9	Radiological	III	27	28	Yes
6	**Can**	24	628	M	N/A	No	No	No	Yes	10/8	Radiological	II	72	No	
7	**UK**	25	677	M	7	Yes	Yes	No	No	0/7	Radiological	II	16	No	
8	**Can**	25	677	M	10	No	Yes	Yes	Yes	8/8	Radiological	III	15	17	Yes
9	**Can**	25	790	F	4	No	No	Yes	Yes	8/4	Clinical	II	40	No	
10	**Can**	24	882	F	5	No	No	No	No	4/5	Radiological	III	17	19	Yes
11	**UK**	26	955	F	4	No	No	Yes	No	7/4	Radiological	II	27	No	
12	**UK**	26	750	M	5	No	No	Yes	Yes	6/6	Radiological	II	7	No	
13	**UK**	27	900	F	2	No	No	No	No	0/6	Radiological	III	29	29	Yes
14	**Can**	27	828	F	4	No	No	No	No	7/4	Radiological	II	75	No	
15	**Can**	27	1040	M	2	No	No	No	No	1/5	Radiological	II	11	No	
16	**Can**	27	1005	F	1	No	No	No	No	10/3	Surgical	III	11	11	Yes
17	**Can**	27	1220	F	1	No	No	No	No	0/0	Radiological	II	27	No	
18	**UK**	28	1380	F	2	No	No	No	No	0/3	Surgical	III	21	No	
19	**UK**	28	1180	F	2	No	No	Yes	No	0/1	Surgical	III	22	No	
20	**UK**	28	1080	F	6	No	No	No	No	1/14	Surgical	III	17	No	
21	**UK**	28	1260	M	1	No	No	No	No	>3/3	NK	III	21	24	Yes
22	**UK**	28	950	M	NK	No	Yes	No	No	NK	Radiological	II	43	No	
23	**UK**	29	1700	F	0	No	No	No	No	0/0	Surgical	III	12	No	
24	**UK**	29	1345	M	1	No	No	No	No	0/0	Surgical	III	8	No	
25	**Can**	29	1360	M	0	No	No	No	No	0/0	Radiological	III	13	14	Yes
26	**UK**	30	1380	M	2	No	No	No	No	3/0	Clinical	II	28	No	
27	**UK**	30	1270	M	1	No	No	No	No	6/0	Radiological	II	23	No	
28	**UK**	34	1290	M	1	Yes	No	No	No	0/0	Clinical	II	7	No	

Table 9.40: Characteristics of individual infants that developed NEC

Table 9.41: Feed-related data for individual infants that developed NEC

	Country	Gestation (weeks)	Birth weight (g)	Sex	Stage of NEC	Day of NEC	Day of first feed	First feed	Days of MEN	Early advancing feeds	Day of reaching full feeds	Time from first to full feeds	Maintenance feeds
1	**72 UK**	24	635	M	III	8	6	MEBM	1	MEBM	Died	-	-
2	**248 UK**	24	530	M	III	68	8	MEBM	2	MEBM	27	20	PTF
3	**470UK**	24	590	M	III	12	4	MEBM	2	MEBM	10	7	MEBM
4	**575Can**	24	720	M	III	6	4	MEBM	2	MEBM	71	68	MEBM
5	**666Can**	24	663	M	III	27	2	MEBM	9	MEBM	Died	-	-
6	**677Can**	24	628	M	II	72	7	MEBM	8	MEBM	18	12	MEBM/PTF
7	**462UK**	25	677	M	II	16	4	MEBM	4	MEBM	15	12	MEBM/T/PT
8	**492Can**	25	677	M	III	15	10	MEBM	6	MEBM	Died	-	-
9	**505Can**	25	790	F	II	40	4	PTF	2	MEBM	36	33	PTF
10	**133UK**	26	955	F	II	27	3	MEBM	2	MEBM	9	7	HPF
11	**233UK**	26	750	M	II	7	5	MEBM	2	MEBM	16	12	PTF
12	**388UK**	27	900	F	III	29	5	DEBM	1	MEBM	13	9	MEBM
13	**578Can**	27	828	F	II	75	3	MEBM	2	MEBM	20	18	MEBM
14	**626Can**	27	1040	M	II	11	4	PTF	1	PTF	38	35	PTF/MEBM
15	**627Can**	27	1005	F	III	11	3	PTF	1	PTF/MEBM	9	7	-
16	**694Can**	27	1220	F	II	27	3	MEBM	7	MEBM	23	21	MEBM
17	**46UK**	28	1380	F	III	21	3	TF	2	MEBM/TF	9	7	MEBM/PTF
18	**52UK**	28	1180	F	III	22	1	MEBM	4	MEBM	12	12	MEBM/HPF
19	**86UK**	28	1080	F	III	17	7	MEBM	3	MEBM	NK	-	MEBM
20	**200UK**	28	1260	M	III	21	5	MEBM	4	MEBM/PTF	NK	-	NK
21	**283UK**	28	950	M	II	43	6	MEBM	NK	MEBM	25	20	NK
22	**162UK**	29	1700	F	III	12	2	TF	1	MEBM/TF	5	4	MEBM/TF/HPF/PTF
23	**394UK**	29	1345	M	III	8	1	MEBM	1	MEBM	6	6	MEBM
24	**500Can**	29	1360	M	III	13	2	MEBM	4	MEBM	Died	-	-
25	**31 UK**	30	1380	M	II	28	4	MEBM	1	MEBM	21	18	MEBM
26	**189 UK**	30	1270	M	II	23	2	MEBM	2	MEBM/HPF	11	10	MEBM/HPF/PTF
27	**378UK**	34	1290	M	II	7	2	PTF	1	MEBM/PTF	23	22	MEBM/PTF

	Country	Gestation (weeks)	Birth weight (g)	Sex	Stage of NEC	Day of NEC	Full feeds	Change from EBM	Transfusion within 72hours	H2 antagonists/ prokinetics prior to NEC	Fortifier added within 72 hours	Possible episode of hypoxia-ischaemia
1	**72 UK**	24	635	M	III	8	Died	No	No	No	No	Pulmonary haemorrhage, Day 3
2	**248 UK**	24	530	M	III	68	27	No	No	No	No	
3	**470UK**	24	590	M	III	12	10	No	Yes	No	No	
4	**575Can**	24	720	M	III	6	71	No	No	No	No	Pneumothorax and hypoxia, Day2
5	**666Can**	24	663	M	III	27	Died	No	No	No	No	
6	**677Can**	24	628	M	II	72	18	No	No	Yes	Yes	
7	**462UK**	25	650	M	II	16	15	No	No	No	No	
8	**492Can**	25	677	M	III	15	Died	No	No	Yes	No	
9	**505Can**	25	790	F	II	40	36	Day 29	No	Yes	No	
10	**133UK**	26	955	F	II	27	9	No	Yes	Yes	No	
11	**233UK**	26	750	M	II	7	16	No	No	Yes, day 14	No	Pulmonary haemorrhage, Day 3
12	**388UK**	27	900	F	III	29	13	No	No	No	No	
13	**578Can**	27	828	F	II	75	20	No	No	Yes	Yes	Cardiac arrest and CPR, Day 74
14	**626Can**	27	1040	M	II	11	38	No	No	No	No	
15	**627Can**	27	1005	F	III	11	9	No	No	No	No	
16	**694Can**	27	1220	F	II	27	23	No	No	No	Yes	
17	**46UK**	28	1380	F	III	21	9	Day 10	No	No	No	
18	**52UK**	28	1180	F	III	22	12	No	Yes	No	No	
19	**86UK**	28	1080	F	III	12	NK	No	No	No	No	Pneumothorax / seizures, Day 5
20	**200UK**	28	1260	M	III	21	NK	No	NK	NK	NK	
21	**283UK**	28	950	M	II	43	25	No	No	No	No	
22	**162UK**	29	1700	F	III	12	5	Day 6	No	No	No	
23	**394UK**	29	1345	M	III	8	6	No	No	Yes	No	
24	**500Can**	29	1360	M	III	13	Died	No	No	No	No	
25	**31 UK**	30	1380	M	II	28	21	No	No	No	No	
26	**189 UK**	30	1270	M	II	23	11	Day 17	No	No	Yes	
27	**378UK**	34	1290	M	II	7	23	No	No	No	No	
28	**663Can**	24	882	F	III	17	10	No	No	No	No	

Table 9.42: Other factors present in babies that developed NEC

CHAPTER 10

DISCUSSION

The subject of this thesis is a two-part observational study, conducted in the UK and Canada. A questionnaire survey sent to neonatal clinicians sought to investigate current opinion and reported practice with respect to early enteral feeding of infants born at less than 30 weeks of gestation and/or 1501g birth weight in the UK and Canada. This survey was complemented by a detailed retrospective review of the medical and nursing records of 695 infants admitted to fifteen UK and three Canadian neonatal units.

There have been few recent detailed reports relating to opinions about feeding of preterm infants. Churella *et al* conducted a US survey in 1983[414], but changes in many aspects of neonatal care limit the relevance of this for current practice. In 1987 and 1994, a telephone survey of feeding policies for ventilated preterm infants in 22 UK regional neonatal intensive care units showed fundamental differences between units, in spite of a tendency to more uniform approach over the time period between surveys[415]. More recently, Patole and Muller reported results of a 2001 Australian survey of neonatologists' practice and examined the response to the presence of risk factors for NEC, again showing uncertainty and variation in practice[190]. Holm conducted interviews with 12 medical and nursing clinicians to explore in detail the reasons behind variation in practice between two UK units[416]. The most recent survey was published in 2009 and reported analysis of a 2006 survey of neonatologists, neonatal nurses and dieticians in the US[191]. This survey investigated intentions of clinicians with respect to feeding practice in preterm infants and compared them to published recommendations available at the time. The authors reported on both parenteral and enteral nutrition practices and concluded that regimens that were more appropriate were being used at that time than in previous studies, although the response rate was poor for this survey, raising concerns about non-response bias as highlighted in the following section of this discussion. Other surveys have focused on individual areas of feeding[417 418] or on maternal experiences of feeding preterm infants[419 420].

10.1 Strengths and limitations of the survey

This approach of this study is novel in its ability to explore the complex relationship between available research evidence, clinician opinion and clinical practice. It provided a unique opportunity for direct comparison of practice between two developed countries providing care to similar populations of infants in the context of modern neonatal intensive care.

Double entry of research data represents the "gold standard" but for financial reasons, it was not possible to appoint a second researcher for this study. Extensive and detailed data collection by a single researcher across all included neonatal units in both countries ensured consistency in the approach to data collection and definitions and completeness of data. Previous piloting of the methodology[1] allowed appropriate amendments to be made to the dataset and refinement of data collection methods before embarking on the current survey.

The postal survey is the largest of its kind in the UK and Canada and was distributed to all senior clinicians involved in care of the group of infants of interest. This inclusion of consultant and attending neonatologists ensured that responses were informed and based on a high level of clinical experience. The retrospective review included neonatal units that were representative of the range of neonatal intensive care offered at the current time, in order that the results might be generalisable to the wider neonatal population. All live-born babies meeting the selection criteria, born during the six-month study period, were eligible to be included in the study, allowing data collection from birth for both survivors and non-survivors. To the author's knowledge, the retrospective review represents the largest cross-sectional survey of its kind and this is the only survey to document contemporaneously both reported and actual clinical practice.

A number of limitations to both parts of the survey are acknowledged. The use of a postal survey rather than interviewing of clinicians probably led to poor response rates, in spite of additional attempts to engage non-responders. The overall response rate of 40.7% is lower than might be expected. However, further analysis revealed that 78.4% of all valid responses received were either from tertiary neonatologists or from paediatricians known to have a special interest in neonatology, whilst responses from general paediatricians with only limited responsibilities for neonatal care were fewer. The response rate in this subgroup was 57.3%, which is comparable with response rates to other postal surveys of medical professionals[421-423]. An additional 20 responses were excluded from the analysis as these

clinicians requested that unit-based responses were considered and declined requests to complete individual questionnaires. Asch *et al* examined response rates to postal surveys in published studies and found that, although response rates were poorly reported in many studies, those seen in surveys to physicians were the lowest observed with a mean (SD) response rate of 54 (17)%[421]. Cummings *et al* selected a random sample of 5% of articles published between 1986 and 1995 reporting data from postal questionnaires to doctors[423]. They showed an overall average response rate of 61%, which fell to 52% for studies with more than 1000 observations. This study was updated recently for studies among health professionals published between 1996 and 2005[422]. The results suggested that response rates in doctors had fallen significantly to 57.5% (95% CI: 55.2-59.8%). Previous published postal surveys specifically related to feeding in preterm infants have reported variable response rates: Churella *et al*, 275/702 clinicians (39%)[414]; Patole and Muller 56/80 (70%)[190]; Hans *et al* 176/775 (23%)[191].

A Cochrane systematic review identified a number of ways of increasing response to postal questionnaires[424]. These included the use of financial incentives, recorded delivery, follow-up contact and provision of a second questionnaire, university sponsorship, personalised questionnaires, the provision of a stamped addressed, rather than franked envelope, first class mailing, the suggestion of an obligation to respond and the questionnaire being about an interesting subject. Whilst financial and ethical restrictions prevented the use of first class postage, recorded delivery or monetary incentives, the remaining methods suggested were used in this survey. It is likely that limitation on clinicians' time to complete surveys played a large part in the low response rate seen. However, the increased response rate in clinicians with a declared interest in neonatal medicine suggests that the degree of interest in neonates, and therefore in neonatal feeding, may have played a major part. In fact, the desire to be fully inclusive when distributing the questionnaire may have been detrimental in this respect. If such a survey was to be repeated in the UK, a more selective approach may be prudent. Reasons for differences in response rates observed between UK and Canadian clinicians are speculative, but may be related to the distribution of the questionnaire in Canada by email rather than by post, or to a lack of a feeling of obligation to complete a survey sent by a non-Canadian trainee. Poor response rates raise concerns about non-response bias. In this survey, results are based mainly on responses from those with a specific neonatal interest and may not represent views of clinicians with only limited roles in neonatal care. It is also likely that those with an interest in preterm feeding were over-represented, although this information was not sought. However, since neonatologists in tertiary centres coordinate care for the

majority of high-risk infants, this may not substantially compromise the validity and generalisability of the results. The fact that almost 80% of neonatal units surveyed were represented provides some reassurance, but must be accompanied by the caveat that results also indicated substantial variation in practice within individual units.

The retrospective review was not a population-based study in that it did not include all neonatal units in the two countries. Although ideal, this approach would not have been feasible due to time and cost limitations. A random sample of units in the two countries would also have been preferable, but would also have been prohibitively challenging for similar reasons, particularly in Canada where distances between units are great. An opportunistic approach was therefore adopted, which would allow maximum efficiency of data collection within financial and time constraints. This may have introduced some selection bias, as included units were located within two principal areas of the UK and only one province of Canada. Potential sources of bias may relate to systematic differences in clinical approach in different areas of the country or differences within the maternal or infant population due to ethnic, cultural, socio-economic, environmental or genetic differences. Such elements are likely to be of only modest clinical significance in the UK, where distances are small and most populations of many areas are cosmopolitan. Within the practical constraints associated with conducting the study, units in the UK were chosen to represent urban and rural areas, areas of socioeconomic affluence and deprivation and areas of ethnic diversity. In contrast, populations of different areas of Canada may be significantly different in terms of culture and environment. Data collection in one province may therefore limit the generalisability of the study results to other parts of the country, although widespread integration and movement of populations, particularly to and within large cities such as Toronto means that this effect may be less relevant in modern society than in the past. Similarly, movement of clinicians from one part of Canada to another may lessen the likelihood of systematic differences in clinical management.

There are major limitations associated with any observational and retrospective study design when compared with randomised controlled trials, prospective cohort studies or case-control studies. Crucially, in retrospective reviews, the data collected have been for clinical, rather than research purposes. The researcher must rely on the availability of medical records and make assumptions about the accuracy of recording in the records; incomplete data may lead to bias in the results, depending on the reasons for the unavailability of information. In this study, medical records were unable to be located for 6/701(0.08%) eligible babies. Some of

these records were thought to be under investigation for medico-legal reasons. It is possible that elements of care will have differed substantially in this group from those of babies whose records were retrieved, but this small proportion is unlikely to significantly influence the overall results unless all suffered adverse outcomes associated with feeding practice. This information was not available. Other exclusions occurred prior to analysis because some infants were not representative of the population of interest and others had excessive amounts of missing or uninterpretable data that might unduly influence study results. These numbers were also small (25/701 (3.5%)). Clinical entries in medical records were assumed to be accurate, but unusual entries were verified by cross checking with other entries in notes or discussion with clinicians. Accurate and complete data were therefore available for all or most analyses for 96% of eligible infants.

The issue of confounding limits the conclusions that can be drawn from any retrospective observational study. Whilst attempts were made to obtain information on all potential confounding factors and to control for these in analysis, there may be some unknown or unrecognised factors that were not considered. Birth weight and gestation are probably the most important confounders in this group of babies and these were controlled for mainly by stratification at the time of analysis. Unequal distribution of confounding factors may also have influenced results of comparisons between countries or units. Similarly, unequal numbers of babies in different centres and different countries limits the interpretation of results. This study can at most suggest associations between independent variables and outcomes considered and can in no way establish causality. Nevertheless, the observed associations provide information either to support or question current beliefs and suggest areas for development of further interventional research.

Additional limitations relate to the content of the clinician questionnaire and data collected in the retrospective review, both of which restrict interpretation of the data. Clinicians were asked about clinical practice in relation to feeding in babies of <30 weeks of gestation or 1501g birth weight. It is clear from the variation seen in responses and in the survey of practice that this encompassed too wide a range of babies and that practices probably differed more with gestational age and birth weight than was anticipated. It was not possible to tease out these differences from the questionnaire responses and this limits the ability to compare between reported and actual feeding practice. With respect to the retrospective review, detailed serial data for weight gain were not collected and this makes it impossible to determine whether different feeding practices have significant effects on growth. It had been

intended that robust data about weight gain either at discharge or at a given gestational age, such as 36 weeks would be collected. However, the large number of transfers to other units prior to discharge from hospital made this impossible. Another important outcome, for which data were collected, was the occurrence of infection. However, diagnosis of infection is challenging for a number of reasons. Firstly, signs of sepsis are non-specific in neonates and so antibiotics are frequently administered for clinical suspicion on infection and then discontinued if no organisim is identified on culture. Secondly, sampling of blood and other normally sterile fluids is technically difficult, and the interpretation of culture results is therefore challenging. Therefore, although the presence of culture-positive sepsis was included as an independent variable in regression analyses, it was not deemed appropriate to conduct analyses with sepsis and an outcome variable.

Although this is one of the largest and most detailed surveys to date, the amount of data collection limited the number of babies that could be included by a single researcher. In turn, this limited the number of important outcomes that could be detected within the group of babies. One of the main aims of the study was to document in detail reported and actual feeding practice in UK and neonatal units and this aim was achieved. However, this necessitated a 'trade-off' between detailed data in this aspect of the study and quantity and quality of outcome data. Since data for several thousand babies would probably be needed in an observational study to show robust associations with rare outcomes such as NEC, this ideal type of study, characterised by detailed data and large numbers of outcomes is probably not feasible without substantial funding and collaborative effort. Nevertheless, data collected in this study add to the body of knowledge and serve as a means to highlight areas for further exploration and to inform design of large randomised controlled trials, which are better able to determine cause and effect with relatively small numbers of babies.

10.2 The use of feeding guidelines

There have been no published studies reporting information about the use of clinical guidelines for preterm infant feeding. The North American survey by Hans[191] and Australian survey by Patole[190] questioned neonatologists on their clinical practice but neither study addressed the availability of clinical guidelines for feeding within the units surveyed. The pilot survey of 15 neonatologists in Scotland[1] questioned a single clinician in each unit and it was assumed that the response would represent the unit. The responses suggested that 8/15

(53%) NNUs had written clinical guidelines for some aspect of enteral feeding in preterm neonates. In contrast, this wider survey asked all neonatal clinicians, with a positive response from 59%. Although some variation in responses was anticipated for questions that sought opinions on optimum feeding practice, inconsistency regarding the reporting of availability of written guidelines was unexpected. However, from more than half of the neonatal units included in the survey, Yes/No responses from members of the team were conflicting, implying that substantial numbers of senior clinicians were unaware of the presence of written guidelines in their own neonatal unit. It is also possible that, in units where a single clinician responded, the information provided was inaccurate. Explanations for this might include very recent introduction of guidelines, incomplete dissemination of information among staff or unwillingness of clinicians to recognise and acknowledge such guidance, even if it exists.

Preterm infant feeding is one of the few areas of neonatal medicine in which the use of written guidance and standardised regimens has been examined in relation to outcomes[219]. Although there are limitations to the research, it has been suggested that standardised regimens may be important in reducing NEC. It is perhaps surprising then that the use of unit guidelines may be as low as 10% for some aspects of feeding and that clinicians' knowledge of local guidelines is so limited.

However, the inconsistencies in these results may be simply a reflection of the challenges associated with producing and implementing formal guidelines. Despite the increasing development of clinical guidelines in all branches of medicine, opinion remains varied with respect to their effectiveness in changing clinical practice[425 426]. The success of guideline implementation depends on widespread and effective dissemination within the clinical environment and "buy in" or support of all clinicians. In centres where considerable enthusiasm on the part of one or more clinicians is directed toward the pursuit of excellence in a particular part of practice, such "champions" may strive more than others to develop and implement evidence-based guidelines. This is likely to be the case in centres that go on to examine and publish their experience and this may in part, be responsible for some of the positive results reported in studies of feeding regimens[213-216 219 220]. For areas of practice where evidence is uncontroversial and robust, successful guideline implementation may be easier, but in areas such as preterm feeding, where availability of evidence is poor, variation in opinion is great and results of research inconsistent, it is less simple. Nevertheless, guidelines can represent an effective way of synthesising evidence, where this exists to guide

practice, or of reaching consensus on practice methods where it does not[426]. The widespread use of standardised guidelines is relatively recent and many established clinicians are more used to basing decision-making on years of clinical experience. Cabana *et al* identified seven barriers to adherence to clinical guidelines[427]. These were lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice and external barriers. Few researchers have investigated the adherence to clinical guidelines in neonatal medicine. In a retrospective review, Atkinson *et al* showed only 54% adherence to a guideline for the use of phototherapy in neonates[428]. In a survey (response rate 55%) to assess adherence to the guideline for developmental screening in infants produced by the American Association of Pediatrics, only 23% reported using a defined screening tool, as recommended by the guideline, while 71% carried out screening in a non-standardised way[429]. It therefore seems likely that, even where guidelines are in place for feeding of preterm infants, the extent to which they are followed may be variable. It was not possible to investigate adherence in this study, as copies of neonatal unit feeding guidelines were not obtained to allow comparison with practice.

10.3 Factors influencing feeding practice

Both the postal and retrospective surveys demonstrated the large number of factors that appear to be influential in the process of clinician decision-making to allow attainment of full feeding in vulnerable infants. Some of these factors are more consistent and widespread in their influence than others and these are discussed below.

10.3.1 Type of feed

EBM is recommended as the feed of choice for preterm infants and there are few contraindications to its use[430]. Although evidence from randomised trials is scarce[198 199], the introduction of enteral feeds as early as the first or second day of life does not appear to confer any disadvantage and may be protective against NEC and sepsis[203 204]. In this clinician survey, more than 90% indicated that their preferred time for introduction of breast milk would be during the first 48 hours of life. Since this is the large majority of clinicians, it might reasonably be expected that this would be the intended practice in most neonatal units. However, in the retrospective survey of practice, less than half of all infants surviving to receive some enteral feed were fed on day 1 or day 2 of life and almost one third reached

four or more postnatal days before receiving any milk. Survey respondents indicated that they might delay initiation of feeds for many different reasons. This was in response to direct questioning about factors that have been associated with feeding practice in the published literature. Although more, less or different reasons may have been suggested without these prompts, it is probable that these responses do, in fact, reflect practice at the time of the survey.

In the retrospective review, the use of EBM for the first feed was significantly associated with the timing of feed introduction in all groups and in babies of <1250g birth weight, it was the most significant factor. Feeding with EBM has been associated with improved short- and long-term outcomes[113-116 143-145] and so expression of breast milk is encouraged as early as possible. Mothers of preterm infants say that expressing breast milk is an important way in which they can contribute to their babies' care and some appear to view it as a way of "compensating" for a baby's premature delivery[431]. It is suggested that expression of breast milk should occur on the first day after birth in order to increase the likelihood of establishing breast-feeding in the long term[432]. It is nevertheless common for mothers who intend to breast-feed their premature babies to have trouble in expressing breast milk shortly after delivery. For some, difficulties can be prolonged for several days, because of either maternal illness or poor milk supply. Frequently, beginning enteral feeds in a preterm baby is clinically indicated before the time at which the mother is able to express any or adequate breast milk. In these circumstances, a decision must be taken whether to wait for maternal breast milk or to commence feeds with another type of milk.

Unexpectedly, in this study, the use of EBM for the first feed was associated with later introduction of feeds and this may be related to conscious decisions to wait for breast milk. Of all babies fed within the first 48 hours after birth, only 47% were given maternal breast milk and a further 8% received DEBM. This implies that, although clinicians aspire to start feeds at this early stage, in reality it may prove challenging to obtain expressed breast milk from mothers, or that in some infants the perceived risks of feeding during the first 48 hours, even with EBM, were greater than the risk of delaying. The randomised controlled ADEPT Trial in growth restricted infants of <35 weeks of gestation with abnormal antenatal Doppler studies, currently published in abstract format, reports that of 189 infants recruited to the early feeding arm (feeds started on day 2 of life), 81% received feeds at the specified time and 82% received breast milk as the first feed[433]. However, the proportions of babies that received MEBM and DEBM are not specified in this preliminary report. The early

introduction of feeds did not appear to increase the risk of later NEC. It is likely that many of the infants recruited to this trial would also have had other factors that might lead to delayed feed introduction. Ronnestad also reports that of 462 infants enrolled in a Norwegian study, 61%, 92% and 96% had started feeds with human breast milk by days 1,2 and 3 respectively[201]. This suggests that, even in high-risk infants, it is possible both to obtain breast milk within the first 48 hours and to introduce feeds successfully at this early stage. An additional factor contributing to the studies' success may be that in neonatal units participating in research, there may be a heightened awareness of feeding issues leading to a more proactive approach in encouraging mothers to express breast milk before the first feed. Challenges in the staffing of both neonatal and midwifery units are well-recognised, particularly in the UK, and this is likely to mean that fewer personnel and resources can be devoted as part of routine care to providing prolonged assistance to new mothers to help them to achieve successful and early expression of breast milk.

Infants starting feeds beyond the first five days of life all received MEBM, while those starting feeds earlier variably received preterm, term or hydrolysed protein formula. Feeds used in the absence of breast milk mirrored the reported preferences of clinicians participating in the postal survey and may reflect their consideration of perceived risks and benefits of different feeds although the evidence on which to base such a decision is limited. In infants starting feeds at the end of the first week of life or later, it is likely that this represents a group of particularly high-risk infants and/or reflects a delay whilst awaiting MEBM. This is also broadly in line with the views expressed in the survey indicating that only a minority of clinicians would wait for more than 7 days for MEBM.

In this study, during the build up to full feeds, 64% of infants received EBM as their only milk or received only very small amounts of other milk during the first two days of life. This compares favourably with other studies. Hylander reported that 59% received exclusively breast milk[434]; Furman reported that in her study, 66% received some maternal breast milk[112] and Meinzen-Derr reported that approximately 30% of infants in a study of glutamine supplementation were exclusively breast fed for the first 14 days of life[119]. However, in Ronnestad's study, 92% of infants were receiving MEBM and 6% DEBM at the time of attaining full feeds[201]. The exclusive use of EBM for early feeding was expected to be associated with more rapid feeding, since this is regarded as the most appropriate feed for immature babies and is better tolerated. However, analysis of the number of hours for which feeds were discontinued showed that infants who received exclusively EBM had their feeds

discontinued for a greater period of time overall, suggesting either poorer feed tolerance or the presence of other reasons for feed discontinuation. Regression analysis of the time to full feeds showed differences between the gestational age bands. In infants of 28-29+6 weeks of gestation, EBM was associated with earlier establishment of full feeds. However, there was no association with the time to full feeds in infants of <28 weeks of gestation and in infants of ≥30 weeks of gestation, was unexpectedly associated with increased time to attain full feeds. Most (82%) babies in the lowest gestational age group received exclusive EBM, which may reflect unwillingness of clinicians to use other milks in infants perceived to be at highest risk of NEC and this high proportion in a relatively small group may account for the inability to detect an association. The association with slower feeding in breast-fed babies in the highest gestational age group is difficult to explain and may be a chance finding. However, one might speculate that sick infants or those perceived to be at higher risk of feed intolerance or NEC were preferentially given breast milk, but were also fed more cautiously than those for whom the risk was thought to be lower. Alternatively, it may represent differences in clinical practice between centres in the management of more mature infants and it is interesting to note that within this gestational age group, the effect of the country of neonatal care was highly significant and increased the significance of exclusive breast milk feeding in the regression model.

Data for ongoing maintenance feeds and feeding on discharge were unavailable for many babies who were transferred to other neonatal units before discharge from hospital. However, from the available data, less than 40% were receiving breast milk at the time of leaving the neonatal unit surveyed. Most commonly, breast milk feeds were changed to preterm formula. Schanler's randomised trial of DEBM or preterm formula to supplement MEBM feeding found that 21% of infants in the DEBM group required a change to preterm formula because of poor weight gain[118]. It was not possible to ascertain the reasons for change in milk in this study, but it appeared that a change to preterm formula was most common in units where HMF was not used, suggesting that poor weight gain may have been the primary reason. However, it is interesting to note that the unit with the highest proportion of exclusively breast fed babies did not introduce HMF for these babies. This highlights current uncertainties about the most appropriate way in which to promote growth in low birth weight infants. Although HMF is widely used, this is not universal and some clinicians prefer milk substitution or increase in volumes. The timing of introduction of fortifier was not investigated in this study, but is also likely to be very variable. The use of hydrolysed formula varied between the birth weight and gestational age groups. Since this type of feed

tends to be utilized to minimize feed intolerance in ELBW babies this might be expected to fall with increasing birth weight, but the highest proportion of babies is in the middle group, which is difficult to explain and suggests that the use of hydrolysed formula may be related to factors other than birth weight.

10.3.2 Severity of illness

In the retrospective review of feeding records, a number of additional factors were independently associated with delay in feed initiation, including lower birth weight, ventilation, acidosis, inotropic support and sedation. Systemic sepsis in preterm infants is regarded as extremely significant and usually represents serious illness. A definite clinical suspicion of severe infection in this group of babies can therefore be regarded as a marker of severity of illness. Established sepsis is often characterised by hypotension and treatment with inotropic drugs; these three factors are therefore closely related. However, low blood pressure requiring treatment may occur for reasons other than infection. Canadian clinicians appeared to be more likely to delay the introduction of feeds in the presence of any of these three factors. Approximately half of the respondents to the postal survey highlighted the use of inotropes as an independent reason to delay initiation or slow feed advancement. In contrast, less than one quarter identified the other factors. Most of these factors in the babies of <30 weeks of gestation appear to relate to early severity of illness and so may occur together. The significant association of higher CRIB score with later feed initiation in these babies supports this hypothesis. It is likely that many acutely unwell babies had feeds delayed until greater stability was achieved. By the time feeds began to advance therefore, a number of these factors were probably no longer present. However, continuing or renewed need for respiratory support is probably a reasonable marker of severity of ongoing or new illness. The effects of this appeared to influence the rate of advancement of feeds in the least mature babies, with a greater need for either mechanical ventilation or nCPAP particularly associated with slower feeding. In larger and more mature babies, ventilation and other markers of illness were not associated with the time to attain full feeds and this is likely to be due to smaller numbers of very sick babies in this group. Since these more mature babies tend to be fed earlier and more rapidly, the relatively greater influence of other factors, such as feed intolerance, in increasing time to full feeds is perhaps to be expected.

10.3.3 Opiate sedation

The use of opiate sedation was associated with later initiation of feeding in babies with birth weight ≥1250g. In years leading up to this study, the routine use of opiate sedation in very preterm ventilated infants had become increasingly prominent despite the still sparse evidence regarding either efficacy or safety[435 436]. The smallest and least mature babies often require long periods of ventilation and it is likely that many of these infants would be receiving sedation. Although this hypothesis was not investigated, it may explain the inability to detect an association with feeding in these groups. In larger preterm babies, sedation may be reserved for the sickest infants and the association with later feeding may reflect this confounding. Although only a small proportion of clinicians in the postal survey indicated that they would delay feeds solely because of sedation, it was the most highly significant factor in babies of ≥1250g and an independent effect is plausible. Opiates are known to slow gut motility[437] and in neonates, this might increase gastric residual volumes, a factor which was considered important by the majority of clinicians when making decisions about feed progression. Morphine has been associated with delay in starting feeds in a secondary analysis of data from the NEOPAIN (Neurologic Outcomes and Pre- emptive Analgesia In Neonates) Trial of morphine versus placebo in preterm ventilated infants[438]. Babies randomised to receive morphine started and achieved full feeds later and there was a relationship between increasing doses of morphine and later feed initiation. This study also found a statistically significant effect of opiate sedation on the time to full feeds, but this was confined to infants of <28 weeks gestation and may be related to a greater ongoing need for ventilation in this group.

10.3.4 IUGR and abnormal antenatal Doppler studies

Almost three quarters of the clinicians surveyed highlighted abnormal antenatal Doppler studies and less commonly IUGR as reasons for delaying introduction of feeds. Even larger proportions would slow the rate of increase in the presence of these factors. This is unsurprising, since multiple small and large observational studies over many years have shown an increased risk of NEC in growth restricted infants[88 98 439] and in particular in those with absent or reversed end diastolic flow antenatally[83 94 97]. In the light of such studies, recommendations have been made for cautious feeding in these infants[440]. In the review of records, abnormal Doppler studies were related to later introduction of feeds overall

although this did not reach statistical significance in the models for individual gestational age bands. Abnormal antenatal Doppler studies were reported more commonly in UK than in Canadian infants. Whilst the difference may be real, it is more likely that this relates to inconsistent documentation of results of antenatal Doppler findings in neonatal medical records and differences in obstetric practice in measuring umbilical vessel Doppler flow. Variability in reporting was evident in both countries. Since maternal records were not examined to ascertain the true number of women having this investigation, it is therefore likely that the actual number may be higher in one or both countries and that the effect of this on the timing of feed initiation may be greater than suggested. The finding that IUGR babies started feeds earlier than AGA babies was surprising. However, since the majority of growth restricted babies were in the highest gestational age band in both countries this may be subject to confounding by gestational age. Neither IUGR nor abnormal Dopplers was associated with an increased time to attain full feed volumes. In his prospective feeding trial, Mihatsch also found no difference in either the time of starting feeds or rate of increase in growth-restricted babies and concluded that it was unnecessary for special feeding protocols to be developed for these babies[251]. However, from the survey of clinicians it seemed that these were the commonest reasons for developing specific guidelines in both UK and Canadian neonatal units. The recently completed ADEPT Trial is the first prospective randomised controlled study to investigate the effects of different timing of introduction of feeding in preterm growth restricted infants. Infants were fed on the second or sixth day of life and feeds were increased according to a standardised regimen[253 433]. Preliminary reports suggest no difference in adverse outcomes between the groups but early fed babies achieved full feeds 3 days earlier than those fed late[413].

10.3.5 Minimal enteral nutrition

In 1999, Kliegman stated that "gastrointestinal priming must now become the standard of care for very low birth weight infants"[441]. Responses to the postal questionnaire indicated that approximately 40-60% of UK neonatal units and 40-75% of Canadian units used a defined MEN regimen, although details of these regimens were not sought. This is a somewhat smaller proportion than indicated in the 2001 Australian[190] and 2006 USA[191] surveys, in which more than 80% of respondents said that they used MEN in ELBW and extremely preterm infants. The intended duration of MEN reported in these surveys was variable, suggesting that infants in these countries may receive MEN for between 0 and 15

days. MEN was undefined in the American survey. In the Australian survey, three slightly different definitions were used (encompassing volumes between 1ml and 30ml or 30ml/kg/day) reflecting current uncertainty about optimum practice. In this review of UK and Canadian practice in 2004, the definition used was <25ml/kg/24 hours prior to attempts to increase feed volumes; this falls within generally accepted parameters. Sixty-seven percent of infants received MEN volumes for two or more days and the variation in the duration of MEN observed was 1-16 days, similar to that reported in the previous survey. This suggests that inconsistency may be widespread across all countries offering neonatal intensive care to preterm infants and that clinical practice probably did not change substantially between 2001 and 2006. It is notable, however, that the practice of MEN appears to have been widely endorsed and adopted by clinicians despite lack of convincing evidence of benefit and lack of consistent guidance on how to employ this strategy of feeding. The endorsement of MEN in principle is clear from the reported intentions of neonatal clinicians in three separate surveys. However, it is less certain that the results of the retrospective review reflect a positive stance in clinical practice, as it is impossible to ascertain how many infants were maintained on MEN volumes by intent and how many by default because of failure in attempts to increase feeds or concerns about the clinical status of infants. Without clear guidance based on sound evidence from large studies, decision-making is likely to differ between clinicians and to be based on the modest experience of any individual clinician or neonatal unit of caring for a relatively small number of high-risk infants.

A longer duration of low volume feeds would be expected to be associated with a longer time to attain full feeds. The number of days of MEN was highly significantly associated with slower feed advancement in infants >28 weeks, but did not quite reach statistical significance in the least mature infants and it is likely that this may be due to smaller numbers in this group and more consistent use of minimal feed volumes in higher risk infants.

10.3.6 Signs of intra-abdominal pathology

Concerns about intra-abdominal pathology were not associated with the time of initiation of feeds. Signs that would have prompted 60-90% of clinicians in the survey to delay feed initiation were abdominal tenderness, large gastric aspirates, bloody stools and severe

abdominal distension. Abdominal distension in preterm infants is common, and its identification is highly subjective and subject to inter-observer variability, so although there is a highly statistically significant difference in this between the two countries studied, this finding may not be completely robust. The presence of abdominal signs before feeding would be likely to indicate early NEC, bowel obstruction or other bowel pathology, but none of these were recorded as being present in the infants studied. In contrast, and as expected, the presence of signs of intra-abdominal pathology explained much of the variation in the time taken for babies to reach full feeds. Variables showing strongest associations in the entire group of babies were large or bilious aspirates, abdominal distension and Stage I NEC, all of which are closely related indicators of potential intra-abdominal pathology, and which substantial numbers of clinicians highlighted in the postal survey. In this analysis, gastric aspirate volumes of >2ml were regarded as "large", although responses from clinicians to the survey question indicated that many would have lower or higher thresholds than this for slowing or discontinuing feeds. It may be that clinicians make judgements based on the cumulative effects of a number of indicators, or that the significance of gastric aspirate volumes are more related to the size or gestation of the baby in question. Analysis according to gestational age bands showed a gradient in the time to full feeds from the most to the least immature and signs of abdominal pathology were significantly associated with increasing time to full feeds across all gestational ages. Whilst other factors previously mentioned were more significant in the lowest gestational age band, the influence of gastric residuals and abdominal distension became more significant with increasing gestational age and in infants ≥30 weeks of gestation, all significant contributors to the regression model were related to feeding practice or to potential signs of gut pathology. Reasons for this are speculative, but may include earlier and more rapid feeding in larger and more mature preterm infants with associated feed intolerance, a relatively lower occurrence of other pathologies such as respiratory illness in this group or differences in clinical practice between centres. It is also possible that the effect may be exerted by a small number of unusual infants, although examination of outliers for all parameters did not reveal any factors that suggested that exclusion from analysis was necessary.

The importance of gastric residual volumes as a sign of gastrointestinal pathology has been debated[289-291 293] and it has been suggested that volumes of up to 5ml may not be significant in indicating feed intolerance[290]. There is no consensus on what constitutes a significant residual volume, limited understanding of what it represents and little guidance on the appropriate management in the presence of large residual volumes[442]. Nevertheless, the

presence of gastric aspirates in excess of 2ml was the factor highlighted most consistently by clinicians in both the UK and Canada as a reason to slow or discontinue feeds. In the review of infant feeding it was very significantly associated with later attainment of full feeds. Large or bilious gastric aspirates were the most common reasons for discontinuation of enteral feeds in infants receiving either advancing or full feed volumes and affected the largest proportion of infants in the study.

10.3.7 Feed volumes and frequency

Responses to the postal survey indicated wide variation in the volume and frequency of milk given at the time of feed initiation. The review of clinical practice showed similar variation that encompassed the range of volumes and frequencies suggested by respondents to the survey. Standardised regimens that have been reported are few and not all authors have specified feed volumes and frequency used. Brown and Sweet gave 2, 3 or 4ml sterile water at 2 hourly intervals, depending on birth weight[213]; Kamitsuka *et al* used 3 - 4 ml breast milk or diluted formula every 3 hours[215]; Patole *et al* used 0.5-1ml every hour[220]; Kuzma-O'Reilly *et al* suggested "small bolus feedings at intervals of every 3 to 8 hours"[218]; Spritzer *et al* are unclear about volumes and frequency of feeds in their report[214]. In this survey, the largest proportion of clinicians (60%) stated that they would use volumes of 0.5-1ml and the most common frequency suggested was hourly (47%). However, variation did not appear to be strongly related to the influence of birth weight, gestation or severity of illness. In the absence of published guidance on this aspect of feeding, it seems likely that such variation results from personal experience or usual practice in units, as well as from consideration of other risk factors in individual infants and availability of maternal breast milk during the first few days of feeding.

10.3.8 Other factors

Data for other factors that have less commonly been associated with NEC and differences in feeding practice were also collected. Others have noted differences in feed tolerance and the time to achieve full feeds between babies receiving continuous feeds or bolus feeds, although study results have been conflicting[182 300-302]. No association was seen in this study, but the number of babies fed continuously was small. Transpyloric feeding has also been previously

examined with respect to feed tolerance and weight gain[304-306], but in this study, no baby was fed using this method. Since others have also shown adverse effects with transpyloric feeding[308-312], this finding probably reflects the decreased use of this method in preterm infants in the light of evidence. However, anecdotal reports suggest that in some centres transpyloric feeding is still used in babies with refractory feeding tolerance, so it may be that this survey of a relatively small number of neonatal units does not fully reflect current practice.

10.4 Feed intolerance and gastro-oesophageal reflux

Clinicians participating in the postal survey were not questioned about their practice with respect to gastro-oesophageal reflux. However, in the light of reports that, despite a dearth of evidence of efficacy or safety, drug treatment for this condition was common in neonatal units[315 329], data for the use of anti-reflux medications were collected. This confirmed that all of these medications were prescribed amongst babies in this study. H_2 receptor antagonists were the most commonly prescribed and were used in 10-11% of babies. However, patterns of prescribing differed between the two countries and details of these differences are described in a later section.

10.5 Necrotising enterocolitis

Stage II or stage III NEC affected 4.4% of babies in this study. This proportion is in line with other reports that range from 3% to 18%[65 69 245 443]. Stage II disease occurred in almost 2% of babies and Stage III in 2.5%. Mortality among infants who developed NEC was 32%, but that due directly to NEC was 28.5% compared with 10% in infants who did not develop NEC. This proportion of deaths also falls within previously reported range of 12-50%[64 66 69 443 444]. This study confirms the most significant findings of other studies, that the rate of NEC is inversely proportional to gestation at birth and birth weight. It also demonstrates an association between NEC and increased severity of illness. There was an association between NEC and IUGR, but not the presence of abnormal Doppler studies although, as discussed previously, the number of babies with abnormal dopplers may be underestimated in one or both groups.

The single factor that has been suggested to reduce the risk of NEC is the use of EBM for early enteral feeding. A number of studies found that any breast milk was protective and that increasing proportions of feed given as breast milk increased the protective effect. However, the results of this study do not support those findings

There was no significant increase in NEC in babies with a PDA or those treated with indomethacin. In contrast to other studies, NEC was associated with later initiation of feeds and a longer time to progress to full feeds. Studies examining the relationship between umbilical catheterisation and NEC have shown variable results, with some showing a strong association and others no relationship. In this study, on univariate analysis, there was a significant relationship between increasing duration of umbilical catheterisation with UVC or UAC, but the relationship was stronger with UAC. Some have suggested that UACs should be removed after a maximum of 5-7 days or before commencing enteral feeds, but others have refuted this recommendation. In this study, nine infants were fed with a UAC in place and seven infants had UACs for eight or more days. In a further 11 babies, UACs were removed on the first day of feeding. Although this association supports the findings of other studies, also in common with other studies, numbers of infants were small and this may represent a Type II error. In a logistic regression analysis including gestational age, infants of lower gestation and those who had a shorter period of MEN had significantly increased odds of developing NEC, while those who took longer to reach full feeds and those who received indomethacin had decreased odds. The presence of umbilical catheters was not significantly associated after adjustment for other factors. The association with shorter duration of MEN supports the findings of Henderson et al[187] who showed a similar relationship in their case-control study. Although more rapid feeding has been proposed as a factor that increases the risk of NEC, this is not seen in the study. The rate of increase of feeds was not studied specifically and it may be that this is more related to the occurrence of NEC than the time to reach full enteral feeds, which also includes the period of minimal enteral nutrition.

Infants with stage II and III disease were similar in all characteristics except the rate of feed advancement. Infants who developed stage III NEC had been fed significantly more rapidly than those with stage II disease and on average achieved full feeds within approximately half the number of days. This is intriguing and is supportive of others' findings that NEC is associated with more rapid feed advancement, although few have reported differences between the stages of NEC. The fact that rate of feed advancement was not more rapid in

infants with either stage of NEC compared with those without NEC suggests that this may be a spurious finding more related to small numbers or outliers. However, it is interesting to note that, while many researchers are urging caution in the rate of advancement of feeds in high-risk babies, in this study, 95 (14%) babies of <30 weeks of gestation reached full feeds by the tenth day of life and 50 (7.5%) advanced to full feed volumes in seven days or less. The small number of infants developing NEC meant that further analysis with adjustment for other relevant factors was not appropriate.

10.6 Reported and actual clinical practice

There are few opportunities to determine to what extent clinicians' day-to-day practice reflects their opinions of optimum practice. Although the retrospective review of practice involved only a limited number of neonatal units, these were felt to be representative of practice generally in the UK and Ontario, although perhaps not the whole of Canada. The postal survey sought opinion from every clinician and in spite of the modest response rate, most neonatal units were represented suggesting that the responses obtained generally reflect the variation of opinion within the whole body of neonatologists.

Clinician opinion is influenced by many different factors including awareness of published evidence, previous personal experience and education, anecdote and, where guidelines are in place, consensus between fellow clinicians. Whether these opinions translate into practice that is reflective of the opinion depends on a further large number of factors that are related to the condition of individual babies, the beliefs and opinions of the babies' parents and external influences within neonatal units such as availability of staff, equipment and drugs. Some of these factors, such as the prescription of drugs or the use of different feeds are within the control of the clinician, but others, such as change in a baby's condition are to greater or lesser extents, not amenable to change.

In spite of the fact that, in this survey, the use of written guidance was sparse and knowledge of the availability of guidelines was inconsistent, clinicians were willing to report their usual practice and personal opinions with respect to feeding of preterm infants. Results indicated wide variation, but for some areas of practice, agreement of opinions was almost 100%. Since the fear of NEC seems to be universally instrumental in guiding feeding practice, it is not surprising that such agreement was most clearly evident in consideration of signs

indicative of suspected or proven NEC. Interestingly, for most areas of practice only small proportions of clinicians identified factors that would influence their decision-making. The fact that such a wide range of factors was felt to be important by between 3% and 90% of clinicians shows the broad range of influences on feeding. Although there were differences in the proportion of clinicians identifying factors as important influences, broadly speaking, there was a large amount of agreement within the body of clinicians from each country. Many of these opinions were in fact reflected in the observed clinical practice. Perhaps the clearest reflection of opinion in practice is seen in the extremes of practice and where opinion appears to differ significantly between countries. Examples of this are in the management of feeds in babies receiving indomethacin or blood transfusion, where both opinion and practice are confined to only one country.

Broad variation in opinion exists, and it appears that this does translate directly into similar variation in clinical practice. This supports the hypothesis at the start of the study. Where extremes exist, clinicians do not appear to think and act in isolation, but rather a particular practice is seen to be part of the practice of a small number of clinicians as part of a whole spectrum. It is likely that the variation seen does, therefore, represent the differing views and intentions of clinicians rather than unplanned and unpredictable behaviour. This is reassuring in that neonatal feeding is subject to some common 'rules' and consistency, although given the wide variation and lack of evidence, it is sometimes difficult to understand on what basis these 'rules' are founded.

10.7 Comparison between UK and Canadian practice

This is the first detailed comparison of feeding practice between two countries. Some interesting differences were seen between the UK and Canadian clinicians, both in the response to the postal survey and in the observational study of clinical practice.

A number of differences between the two countries were seen for the occurrence at the start of feeding of a number of factors that might indirectly or directly affect initiation, advancement or discontinuation of enteral feeds (Table x.x). These differences may reflect differences in the population of babies or systematic differences in practice. The larger number of Canadian infants having mechanical ventilation and requiring umbilical catheters may reflect either greater severity of illness in the Canadian group, or difference in clinical

management of respiratory disease. Similarly, the difference in PDA may relate either to lower gestational age or the availability of echocardiography to make the diagnosis. In contrast, the use of sedation and indomethacin are likely to reflect true differences in clinical practice between the countries. In particular, the figures for PDA and indomethacin use in Canada suggest that some infants were treated prophylactically. Although no information was specifically obtained about indomethacin doses and whether short or prolonged courses were given, inspection of the data suggests that indomethacin more likely to be given earlier and for shorter, but sometimes repeated courses in comparison with practice in the UK.

Forty percent of Canadian clinicians reported that they would delay feeds whilst awaiting breast milk for only 24 hours or less, compared with only 20% of UK clinicians who, on average, reported that they would be more likely to delay for longer periods of time. Interestingly however, UK infants were more likely than Canadian infants both to be fed earlier and to receive EBM as their first feed, suggesting that this intention may be aspirational rather than feasible in Canada. No Canadian clinician said that they would preferentially use DEBM in this circumstance, reflecting the lack of availability of banked donated EBM in Canada compared with the UK. Whilst 3.5% (n=9) of UK clinicians spontaneously responded that they would be guided by parents' wishes, this was not stated by any in Canada.

UK clinicians suggested that they were more likely than Canadian clinicians both to delay feed introduction and slow the rate of advancement for babies with absent or reversed end diastolic flow. A greater proportion of Canadian clinicians reported that they would delay, slow or discontinue feeds for babies having pharmacological paralysis and indomethacin treatment. No Canadian clinician cited blood transfusion as a reason to change feeding regimens. However, 6% of UK clinicians surveyed would do this and 9% would discontinue feeds. Although only small proportions in both countries would be influenced by the use of sedation, a greater proportion of Canadian than UK clinicians reported delaying and slowing feeds in sedated infants. Whilst there was agreement with respect to most indicators of abdominal pathology, a greater proportion would delay, slow or discontinue feeds in the presence of mild abdominal distension in the UK than in Canada. Larger proportions of UK than Canadian clinicians would interrupt enteral feeding in infants displaying signs of respiratory distress or requiring mechanical ventilation.

The effect of differences in practice by country of neonatal care was evident in the retrospective review of medical records. Regression analysis confirmed that Canadian infants started feeds later than infants in UK units and that this was significant independent effect, even after controlling for birth weight and other potentially influencing factors. This was in keeping with the hypothesis. Analysis by gestational age band further explored the influence of international differences and this suggested that differences in clinical practice might have exerted a greater effect in more mature infants. In the absence of documented reasons for delay in initiation of feeds, it is difficult to untangle individual effects that may represent fundamental differences in practice. Although the effect of country accounted for only approximately 3% of the variation in timing of feed initiation, this may nevertheless be a clinically significant effect.

Infants in Canadian centres progressed from first to full enteral feeds significantly more slowly than UK infants and this was in keeping with expectation. This also showed significance in the regression model, but again, the largest effect of country was exerted in the most mature babies although the effect approached statistical significance in the least mature babies. Contributors to this variation can be identified from examination of the documented reasons for delaying discontinuing either during minimal or advancing feeds. The most striking differences between the countries mirror the reports of respondents to the survey. Feeds were much more likely to be discontinued during indomethacin treatment in Canadian compared with UK infants both during minimal feeding (46.7% v 3.8%) and advancing feeds (17.5% v 2.6%). A greater proportion of Canadian infants also had feeds discontinued for suspected sepsis (6.8 v 1.6). In the UK, clinicians stopped feeds for abdominal distension during minimal feeding in a larger proportion of babies (24% v 4.4%) although the proportions stopping feeds for this reason during advancement of feeds was similar for both countries. No Canadian infant had feeds discontinued during blood transfusion in contrast with almost 3% of UK infants. UK clinicians also omitted feeds more frequently in the absence of breast milk (8% compared with <1% in Canada). Similar proportions of infants had feeds stopped for respiratory deterioration and neither sedation nor paralysis was documented as a reason for feeds being stopped in data for either country. Other factors did not substantially vary between the two countries.

Differences also emerged in patterns of feeding. As anticipated from the results of the clinician survey, DEBM and hydrolysed protein formula were rarely used for Canadian infants. In contrast, hydrolysed formula was commonly used in the UK and appeared to be

the feed of choice in some units where DEBM was not in use and where MEBM was unavailable or insufficient. UK infants were more likely than Canadian infants to receive EBM as their early feeds. However, this did not translate into a high proportion of infants established on exclusive breast milk feeds as many changed to either mixed feeding or exclusive preterm formula feeding shortly after attaining full feed volumes. Reasons for this change were not documented, but since this pattern of feeding was more prominent in units that did not use HMF in any of their babies, it seems most likely that it was to promote weight gain. The perceived benefits of this over HMF are unclear, but the practice may have other disadvantages in addition to the possible increased risk of NEC. Provision of her breast milk is often perceived by the mother of a preterm baby as a very basic and positive aspect of care in an environment where the ability of a mother to care for her baby directly is limited. Removing this opportunity may have adverse psychological effects on the mother and send mixed or adverse messages about the importance and adequacy of her breast milk for her baby.

Unexpectedly, the pattern of feeding in Canadian infants was completely different and almost the reverse of that in the UK. Although many infants received a small amount of formula at the start of enteral feeding, EBM was introduced early and the babies then progressed to establish full feeds with EBM. This led to a greater proportion of Canadian infants than UK infants establishing exclusive breast-feeding. Mixed feeding with EBM and preterm formula during the first few days of life was uncommon in the UK. In contrast, a large proportion of babies in Canadian centres received both types of feed from the outset. As a result, a greater proportion of Canadian infants overall received some or all breast milk during their neonatal stay. These differences are intriguing and difficult to explain based on the limited evidence available for type of feed. One might speculate that maternal and/or cultural elements play a part in this and it may reflect a greater desire to breast feed in Canadian women, compared with UK women. Maternal details were not recorded so this hypothesis cannot be explored. Differences in clinician attitudes might also explain these differences. If so, this would perhaps suggest that UK clinicians are more focused on the potential to reduce the risk of NEC or other pathology by early feeding with EBM, whereas Canadian clinicians aim for the establishment of long-term breast-feeding. It is likely that both might contribute in part, as may other unidentified reasons, but there is little evidence that one approach or the other is better or leads to improved short- or long-term outcomes.

Although infants in both the UK and Canada received treatment for gastro-oesophageal reflux, patterns of prescribing were very different between the two countries. Gaviscon and feed thickeners were not used in any Canadian infant, but were used in 14% and 3% of UK infants respectively. Domperidone and H_2 receptor antagonists were used slightly more commonly in the UK, whereas metoclopramide was given to 3% of Canadian, compared with no UK infants. Such differences in practice are not easy to explain and cannot simply be ascribed to differences in availability of evidence or products. Although reasons can only be speculative, it seems likely that differences emerge due to long-standing local practice or to varying interpretation of evidence supporting or refuting different practices.

10.8 Implications of variation in clinical practice

The results of this survey confirms the findings of the Scottish pilot survey[1 2] that extensive variation in clinical practice exists between and within neonatal units in the UK for almost every area of enteral feeding and suggests that similar or greater variation exists between and within different countries. Sources of variation are many and some of this is undoubtedly related to the diverse and vulnerable population for which neonatologists care. Many of the differences in practice are likely to have arisen with the rapid advancement of knowledge in this relatively young specialty. Eagerness to enhance care and improve survival and long-term outcomes of infants has led to the implementation of many different strategies without the benefit of a strong evidence base, which would take many years to amass. Research that has been conducted has struggled to show clear differences between methods, either due, on many occasions, to small numbers or challenges in study design and methodology. Study results can be interpreted in different ways and influences on practice are equally varied. Uncertainty and confusion are common. Neonatal clinicians and teams therefore continue to practice, in some cases using quite different methods, yet without any clearly demonstrable differences in overall outcomes. It is difficult, therefore, to suggest that one or other feeding strategy is optimum, or that another is suboptimal; one must ultimately ask the question of whether changes and differences in detail of enteral feeding are worth investigating or whether, in fact, there is little to be gained by manipulation of this kind. However, although NEC is a rare illness affecting only a minority of an already small population, its devastating effects are clear and it is one of the most striking inadequacies in our medical knowledge, in terms of causation, prevention and management. Few clinicians would not consider the impact of this disease when choosing the method of enteral feeding for a high-risk infant and

it will continue to dominate clinical practice until our understanding of the disease is clearer. Similarly, few researchers would pass by an opportunity to improve this understanding in some way. The search for optimum feeding strategies for preterm infants is likely to continue and until more robust evidence is produced, variation in practice between individuals and institutions variation will exert effects on outcomes that are yet to be effectively elucidated and measured, but that may have highly significant effects on morbidity or mortality for individual infants or groups of infants.

10.9 Implications for future research

This survey was conducted in 2004, but there is little to suggest that feeding practice has substantially changed or that large amounts of new evidence have become available since that time. Indeed, similar questions are still debated today as then and the gaps in our knowledge persist. The need for further research to guide clinical practice and minimise risk in the most vulnerable infants remains. Important research questions are best answered with large randomised controlled trials, yet such trials have been very few in the recent past.

Results from the recent ADEPT Trial[433] will be a welcome addition to the body of knowledge in the UK and this appropriately powered trial should provide useful and robust information about timing of feed introduction in the highest risk growth restricted infants. ADEPT began in the UK at around the same time as this survey was conducted and arms of the study were chosen to reflect reported practice in a regional survey in the UK[96]. Are these results, therefore, relevant for clinicians in other countries? This survey would suggest that perhaps they are not; as this was one area of practice where clinicians from Canada reported that they would not necessarily respond to the scenario of antenatally diagnosed absent or reversed end diastolic flow in the same way as those in the UK. Are clinicians likely to respond to published results of trials by changing their clinical practice? Clinicians in the UK have invested a great deal of time and effort in supporting and participating in this trial, so they are likely to seek out and modify practice on the basis of the results if appropriate. This may not be the case internationally. Time will tell, but the enormous variation in both opinion and practice, seen between and within units and countries in this survey, does not suggest universal adherence either to published evidence or even to local guidelines where either is available.

Most importantly, for research to be taken seriously and for it to be successful in changing practice it needs to ask unanswered questions that are important to large numbers of clinicians and their patients. In addition, it needs to address the most important outcomes and those that substantially influence clinical practice. The research methods need to be feasible and the results as generalisable as possible. In no area of neonatology are these research challenges greater than in enteral feeding. Perhaps one of the greatest challenges in modern neonatal medicine is the prevention of NEC. Advances in antenatal care and respiratory care have led to prolonged survival of some of the highest risk infants, only for significant numbers to die from the effects of NEC at a stage in their neonatal course when they are more stable and, to their parents, appear to be "out of danger". We urgently need answers to the question "How do we prevent or minimise the risk of NEC in preterm neonates?" and it is unlikely that any clinician in the world would dispute the importance of this.

However, surveys such as this serve to highlight the difficulties in conducting such research. A review of the literature has demonstrated inconsistent or insufficient evidence for many aspects of feeding. The survey of clinicians' feeding intentions indicates lack of awareness of available evidence to guide practice, differences in opinions between clinicians in the same neonatal unit, differences between countries and differences between neonatal units within the same country. Is it surprising, therefore, that the retrospective review of practice shows wide variation in feeding practice that broadly reflects these highly variable views? Perhaps at the root of this problem lies the inconsistent and inadequate evidence, produced by many years of small studies and observational studies (such as this) and inadequately powered to provide robust answers to important questions. Consistent, however, are reports of a large number of potential risk factors that may or may not increase the risk of NEC. There is a need for large, adequately powered and well-designed randomised controlled trials to examine the real contribution, if any, of many of these risk factors to the development of NEC.

The main challenge lies in the fact that NEC is not a common disease, and even in the preterm population can be regarded as a rare outcome. Many studies have included NEC as a secondary outcome but few, if any have contained sufficient numbers of infants to be able to detect a true difference in the occurrence of NEC between intervention groups. Surrogate measures and short-term outcomes such as the time to full feeds, feed tolerance, and occurrence of sepsis have been used in most studies, apparently to circumvent the challenge of recruiting several thousand preterm neonates. Yet from the published literature and from

the work presented in this thesis it seems that the relationship between these surrogate measures and NEC is far from clear. Whilst these measures may be important in their own right from a health economic or service provision perspective, these outcomes are not the outcomes that "drive" clinical practice and the answers provided by such studies will lead neither to clear guidance to refine practice nor to clear reassurance that change is unnecessary.

Future trials should be collaborative and preferably international, acknowledging in the design phase the range and variation in practice that is acceptable to clinicians to produce trial arms that are relevant for the majority. Only using such methods will there be widespread "buy-in" to the trials, which is key to the success and will also ensure maximum impact of significant results in clinical practice after the research is completed. This does not intend to suggest that this approach is straightforward and a great deal of planning is required. Nevertheless, such collaboration and planning has proved possible in a number of parallel trials currently examining oxygen target saturations in preterm infants and for which a prospective meta-analysis is planned in order to provide sufficient power to answer with confidence this important question. The UK[406], Canada[405], the USA and Australia[445] are all involved in this collaborative endeavour. Such an approach might prove helpful in disentangling some of the most taxing dilemmas in enteral feeding in preterm neonates and should address the outcome measures of NEC and/or death and neurodisability as the most important short- and long-term outcomes associated with feeding.

Among potential trials of feeding practice, the effect of the rate of increase of feeds on NEC is probably one of the most pressing issues to address. Rapid feeding has been implicated in the causation of NEC by some researchers[7 197 205 206] and the findings of this survey suggest that there may be an association between the rate of feeding and severity of NEC. Others have found no relationship[207 208]. This survey also suggests that differences between gestational age bands may warrant stratification of trials according to gestational age or birth weight. Without such stratification, it would be challenging to determine appropriate arms for this trial, as caution in the rate of advancement of feeds tends to increase with decreasing gestation and birth weight. Whilst relatively small differences in rate of feed advancement may be clinically significant and therefore appropriate to study, it may be challenging to demonstrate a statistically significant difference in outcomes in the number of babies that might feasibly be recruited, particularly at the lowest gestational ages. In contrast, widely separated groups may be less likely to represent the range of usual practice and may

therefore lack relevance for some clinicians or, more importantly, introduce additional risk at the extremes of practice.

The timing of introduction of feeds has been addressed in the ADEPT trial of feeding in a small group of high-risk growth restricted babies[433]. However, the vast majority of preterm babies do not fall within this group and yet optimum feeding strategies for this much larger and still vulnerable group remain unclear. It is unlikely that the results of the ADEPT Trial are applicable in the wider group, as few clinicians would delay feeds for up to six days in any but the sickest or highest risk infants. Equally, it appears that some do not routinely introduce feeds within two days of birth. However, the clinician survey suggested that there is a preference for earlier feeding among practising neonatologists, although this appears to be difficult to achieve in practice. Clinical equipoise has probably been lost with respect to the timing of introduction of feeds, and according to the retrospective review of practice, feeds were generally given during the first three days of life. If this is universally the case, any further study of this aspect of feeding is not warranted. Previous studies have suggested that feeds were routinely started later in the USA[188], although the most recent survey suggests that here too, practice has changed[191]

The concept of MEN requires further study to determine whether there is any benefit from this type of feeding. Clarity with respect to the optimum time to introduce MEN, optimum volumes and optimum duration of MEN is required. Each of these aspects needs to be studied in its own right, but collaboration between large numbers of units on an international basis might allow investigation of more than one question within the same study framework.

The role of MEBM is probably now established in routine practice. However, in the absence of MEBM, other milks are used and although preterm milk has been quite extensively studied, the appropriate roles of DEBM and hydrolysed protein formula have not been explored in detail. Yet from this survey, it appears that both are commonly used as substitutes for MEBM when this is not available. DEBM is currently only available to a limited number of neonatal units. The introduction of new feeding practices on the basis of limited evidence may lead to different risks or benefits, which may only be attributed with certainty to the feeding within the context of a trial. Maintenance of current breast milk banks and development of further banks should be supported by clear evidence of benefit from the use of donated milk in high-risk infants and of acceptability to mothers of such infants. A reasonable counter-argument might be that the considerable funds required to

support the processing of DEBM could be redirected into provision of support for mothers to begin, establish and maintain breast-feeding of their own infants, as the rates of early breast milk expression in this study suggest that enhancement of this kind of support may be needed.

Some neonatal units preferentially introduce preterm formula where babies' weight gain is poor instead of supplementing MEBM with HMF. This approach has never been subjected to trial and may have unidentified or unrecognised adverse or beneficial effects, which might include a change in the risk of NEC. The use of HMF is, in itself controversial and well-designed studies are required to determine the optimum time of introduction of feeds. Although data for the timing of introduction of HMF have not been analysed, anecdotally, most neonatal units introduce fortification of feeds once full milk feed volumes have been attained. However, this approach is not evidence-based and trials to determine whether earlier introduction of fortifier may confer benefits for growth without increasing the risk of NEC.

The management of PDA clearly varies between clinicians, units and countries in the absence of data from randomised controlled trials. Treatment with indomethacin contributes enormously to the periods of feed discontinuation in spite of a lack of evidence for protection against NEC or other bowel pathology with this approach. Similarly, blood transfusion is managed very differently by different clinicians and centres and also accounts for a substantial amount of withheld feeds in some units. Both of these are common elements of routine neonatal care and therefore could form the basis of a randomised trial to determine with certainty whether feed discontinuation is of true benefit or whether the risks of increased need for central lines and subsequent sepsis might negate any possible benefit.

These suggested trials represent only a small proportion of those that are required, but are probably the most important and the most likely to produce results that might benefit the maximum numbers of babies. Other potentially important interventions including the use of probiotics that are linked to feeding practice, but not addressed in this study are currently under trial. Alternative methodologies such as large, well-designed prospective cohort studies provide useful information about important outcomes, but are expensive and time-consuming. NEC, as a rare outcome, might lend itself to studies using case-control methodology. However, these are challenging to execute and evidence from these is generally regarded as somewhat less robust than that from controlled trials.

10.10 Summary

This study demonstrates that there is wide variation in both opinion and practice among neonatal clinicians in the UK and Canada for most aspects of feeding in preterm and low birth weight infants. It is unlikely that such variation is limited to these two countries and in other parts of the world it may be even more striking. The effects of such variation on important feed-related outcomes are unknown and require further investigation to define optimum strategies to maximise benefit in terms of growth, nutrition and long term neurodevelopmental outcome, whilst minimising the risk of significant morbidity and mortality associated with NEC and infection. Important research questions remain unanswered with respect to the rate of advancement of enteral feeds, timing, volume and duration of MEN and clarification of the relationship between various therapies and NEC. The most robust way of answering such questions is with large randomised controlled trials which may need to be organised on an international scale to produce high quality information to guide clinical practice in the future.

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APPENDICES

APPENDIX 1:

LIST OF ABBREVIATIONS

List of Abbreviations

ADEPT	Abnormal Doppler Enteral Prescription Trial
AEDF	Absent end diastolic flow
ALP	Alkaline phosphatase
ANNP	Advanced neonatal nurse practitioner
BAPM	British Association of Perinatal Medicine
BPD	Bronchopulmonary dysplasia
BPSU	British Paediatric Surveillance Unit
BSID	Bayley Scales of Infant Development
CARD15	Caspase recruitment domain 15
COREC	Central Office for Research Ethics Committees
CPS	Carbamoyl phosphate synthetase
DEBM	Donor expressed breast milk
DHA	Docosahexanoic acid
EBM	Expressed breast milk
EGF	Epidermal growth factor
ELBW	Extremely low birth weight
ET-1	Endothelin - 1
GOR	Gastro-oesophageal reflux
HIV	Human immunodeficiency virus
HMF	Human milk fortifier
ICD-9-CM	International Classification of Diseases 9th revision, Clinical Modification
IL	Interleukin
IUGR	Intrauterine growth restriction
LBW	Low birth weight
LCPUFAs	Long chain polyunsaturated fatty acids
MEBM	Maternal expressed breast milk
MEN	Minimal enteral nutrition
MII	Multichannel intraluminal impedance
MMC	Migrating motor complexes

MREC	**Multicentre Research Ethics Committee**
NEC	**Necrotising enterocolitis**
NICHD	**National Institute of Child Health and Development**
NNU	**Neonatal unit**
NO	**Nitric oxide**
NOD 2	**Nucleotide oligomerization domain 2**
PAF	**Platelet activating factor**
PAF-AH	**Platelet activating factor acetylhydrolase**
PDA	**Patent ductus arteriosus**
PN	**Parenteral nutrition**
REDF	**Reversed end diastolic flow**
RT	**Respiratory therapist**
SIP	**Spontaneous intestinal perforation**
SMA	**Superior mesenteric artery**
SNP	**Single nucleotide polymorphism**
TLRS	**Toll-like receptors**
TNF α	**Tumour necrosis factor - alpha**
UAC	**Umbilical arterial catheter**
UVC	**Umbilical venous catheter**
VLBW	**Very low birth weight**
VON	**Vermont Oxford Network**

APPENDIX 2:

UK AND NORTH AMERICAN NEONATAL FEEDING SURVEY QUESTIONNAIRES

UK NEONATAL FEEDING SURVEY – Clinician Questionnaire

Thank you for agreeing to complete this questionnaire. Please read the following brief notes carefully before answering the questions:

(i) All questions refer to infants born with **birth weight of 1500g or less and / or gestational age of 29 completed weeks (ie. Up to 29 weeks + 6 days) or less.**

(ii) Feeding / feeds refers to **ANY volume given enterally**, whether as part of a gut priming / minimal enteral feeding regimen / trophic feeding regimen, or as volumes intended to provide nutrition.

A. General Information	
A1. Approximately how many babies of ≤ 1500g birth weight or ≤ 29 completed weeks' gestation are looked after per year on your neonatal unit?	_____ babies
A2. Is parenteral nutrition available for babies on your neonatal unit?	Yes / No
A3. Is donor breast milk available for your neonatal unit?	Yes / No
A4. Does your neonatal unit routinely use a <u>defined</u> minimal enteral feeding regimen?	Yes / No

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B. Initiation of Enteral Feeds

B1. **Does your neonatal unit have <u>written</u> guidelines on the initiation of enteral feeds?** Yes / No

B3. **Does your neonatal unit have specific guidelines for the initiation of feeds in particular subgroups of babies?** Yes / No

If No ⇛ Question B5

B4. **For which particular subgroups of babies do you have specific protocols for the initiation of feeds?** *(Please specify)*

....

....

B5. **When breast milk is available AND, <u>in your opinion</u>, there is no specific contraindication to beginning enteral feeds, when do you consider to be the optimal time for introducing enteral feeds?**
(Please circle one of the following)

(i) Day 1 (ie. Day of delivery)

(ii) Day 2

(iii) Day 3 – 4

(iv) Day 5 – 7

(v) > 7 days

B6. **If a mother wishes to express breast milk and the baby is ready to start enteral feeds, how long would you wait for breast milk before starting feeds with another type of milk?** .....

B7. If breast milk is not available, which type of milk is initially given to infants ≤ 1500g birth weight or <29 completed weeks gestation on your neonatal unit?
(Please circle one of the following)

(i) Term formula
(ii) Preterm formula
(iii) Hydrolysed protein formula
(iv) Other (*Please specify)* .....

B8. What is the usual starting volume and frequency for enteral feeds in your neonatal unit? .....

C. Progression to Full Enteral Feeds

C1. Does your neonatal unit have written guidelines on the rate of increase of enteral feeds? Yes / No

C2. Does your neonatal unit have specific guidelines for the rate of increase of feeds in particular subgroups of babies? Yes / No

If No ⇛ Question D1

C3. For which particular subgroups of babies do you have specific protocols for the rate of increase of feeds? *(Please specify)*

....

....

Next Page ⇨

D. Discontinuation of Feeds before Full Enteral Feeding is Established		
D1.	**Does your neonatal unit have <u>written</u> criteria for the temporary discontinuation of enteral feeds?**	Yes / No
D2.	**In your neonatal unit, which members of staff most often make decisions about discontinuing feeds?** *(Please circle all that apply)* (a) Nurse (b) Middle grade doctor (c) SHO (d) Consultant (e) ANNP	

E. Factors influencing feeding practice

Please answer questions numbered E1, E2 and E3 on the next 2 pages by ticking boxes for ALL answers that apply.

Please consider whether the presence of each of the factors IN ISOLATION would influence your practice.

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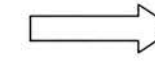
E1. Which of the factors listed below lead you to DELAY STARTING enteral feeds?		E2. Which of the factors below lead you to SLOW THE RATE OF INCREASE of feeds?		E3. Which of the factors listed below lead you to DISCONTINUE enteral feeds?	
(1) History of absent end diastolic flow		(1) History of absent end diastolic flow			
(2) History of reversed end diastolic flow		(2) History of reversed end diastolic flow			
(3) Evidence of perinatal asphyxia		(3) Evidence of perinatal asphyxia			
(4) Presence of UVC		(4) Presence of UVC			
(5) Presence of UAC		(5) Presence of UAC			
(6) Position of UAC		(6) Position of UAC			
(7) Hypotension		(7) Hypotension		(7) Hypotension	
(8) Suspected systemic sepsis		(8) Suspected systemic sepsis		(8) Suspected systemic sepsis	
(9) Sedation		(9) Sedation		(9) Sedation	
(10) Nasal CPAP		(10) Nasal CPAP		(10) Nasal CPAP	
(11) Respiratory disease (not ventilated)		(11) Respiratory disease (not ventilated)		(11) Respiratory disease (not ventilated)	
(12) Acidosis (specify level)		(12) Acidosis (specify level)		(12) Acidosis (specify level)	
(13) Pharmacological paralysis		(13) Pharmacological paralysis		(13) Pharmacological paralysis	
(14) Failure to pass meconium		(14) Failure to pass meconium		(14) Failure to pass meconium	
(15) Polycythemia		(15) Polycythemia		(15) Polycythemia	

Next Page



(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large aspirates *(specify volume)*	
(26) Bilious aspirates	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large aspirates *(specify volume)*	
(26) Bilious aspirates	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large aspirates *(specify volume)*	
(26) Bilious aspirates	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

Thank you

NORTH AMERICAN NEONATAL FEEDING SURVEY – Clinician Questionnaire

Thank you for agreeing to complete this questionnaire. Please read the following brief notes carefully before answering the questions:

(i) All questions refer to infants born with **birth weight of 1500g or less and / or gestational age of 29 completed weeks (ie. Up to 29 weeks + 6 days) or less.**

(ii) Feeding / feeds refers to **ANY volume given enterally**, whether as part of a gut priming / minimal enteral feeding regimen / trophic feeding regimen, or as volumes intended to provide nutrition.

C. General Information	
A1. Approximately how many babies of ≤ 1500g birth weight or ≤ 29 completed weeks' gestation are looked after per year on your neonatal unit?	_____ babies
A2. Is parenteral nutrition available for babies on your neonatal unit?	Yes / No
A3. Is donor (third party) breast milk available for your neonatal unit?	Yes / No
A4. Does your neonatal unit routinely use a <u>defined</u> minimal enteral feeding regimen?	Yes / No

Next page ⇨

B1. **Does your neonatal unit have <u>written</u> guidelines on the initiation of enteral feeds?** Yes / No

B3. **Does your neonatal unit have specific guidelines for the initiation of feeds in particular subgroups of babies?** Yes / No

If No ⇛ Question B5

B4. **For which particular subgroups of babies do you have specific protocols for the initiation of feeds?** *(Please specify)*

....

....

B5. **When breast milk is available AND, <u>in your opinion</u>, there is no specific contraindication to beginning enteral feeds, when do you consider to be the optimal time for introducing enteral feeds?**
(Please circle one of the following)

(i) Day 1 (ie. Day of delivery)

(vi) Day 2

(vii) Day 3 – 4

(viii) Day 5 – 7

(ix) > 7 days

B6. **If a mother wishes to express breast milk and the baby is ready to start enteral feeds, how long would you wait for breast milk before starting feeds with another type of milk?** .....

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or <29 completed weeks gestation on your neonatal unit?
(Please circle one of the following)

(v) Term formula
(vi) Third party donor breast milk
(vii) Preterm formula
(viii) Hydrolysed protein formula
(ix) Other (*Please specify)* .....

B8. What is the usual starting volume and frequency for enteral feeds in your neonatal unit? Volume:.....

Frequency: .....

C. Progression to Full Enteral Feeds

C1. Does your neonatal unit have <u>written</u> guidelines on the rate of increase of enteral feeds? Yes / No

C2. Does your neonatal unit have specific guidelines for the rate of increase of feeds in particular subgroups of babies? Yes / No

If No ⇛ Question D1

C3. For which particular subgroups of babies do you have specific protocols for the rate of increase of feeds? *(Please specify)*

....

....

Next Page ⇨

D. Early Nourishment of Preterm Infants before Full Enteral Feeding is Established

D1.	**Does your neonatal unit have <u>written</u> criteria for the temporary discontinuation of enteral feeds?**	Yes / No
D2.	**In your neonatal unit, which members of staff most often make decisions about discontinuing feeds?** *(Please circle all that apply)* (f) Nurse - RN (g) Neonatal Dietician-Nutritionist (h) Fellow (i) Resident (j) Attending Neonatologist (k) Neonatal Nurse Practitioner	

E. Factors influencing feeding practice

Please answer questions numbered E1, E2 and E3 on the next 2 pages by ticking boxes for ALL answers that apply.

Please consider whether the presence of each of the factors IN ISOLATION would influence your practice.

Next page ⇨

E1. Which of the factors listed below lead you to DELAY STARTING enteral feeds?		E2. Which of the factors below lead you to SLOW THE RATE OF INCREASE of feeds?		E3. Which of the factors listed below lead you to DISCONTINUE enteral feeds?	
(1) History of absent end diastolic flow		(1) History of absent end diastolic flow			
(2) History of reversed end diastolic flow		(2) History of reversed end diastolic flow			
(3) Evidence of perinatal asphyxia		(3) Evidence of perinatal asphyxia			
(4) Presence of UVC		(4) Presence of UVC			
(5) Presence of UAC		(5) Presence of UAC			
(6) Position of UAC		(6) Position of UAC			
(7) Hypotension		(7) Hypotension		(7) Hypotension	
(8) Suspected systemic sepsis		(8) Suspected systemic sepsis		(8) Suspected systemic sepsis	
(9) Sedation		(9) Sedation		(9) Sedation	
(10) Nasal CPAP		(10) Nasal CPAP		(10) Nasal CPAP	
(11) Respiratory disease (not ventilated)		(11) Respiratory disease (not ventilated)		(11) Respiratory disease (not ventilated)	
(12) Acidosis (specify level)		(12) Acidosis (specify level)		(12) Acidosis (specify level)	
(13) Pharmacological paralysis		(13) Pharmacological paralysis		(13) Pharmacological paralysis	
(14) Failure to pass meconium		(14) Failure to pass meconium		(14) Failure to pass meconium	

Next Page ⇨

(15) Polycythemia	
(16) IUGR	
(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large residuals *(specify volume)*	
(26) Bilious residuals	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

(15) Polycythemia	
(16) IUGR	
(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large residuals *(specify volume)*	
(26) Bilious residuals	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

(15) Polycythemia	
(16) IUGR	
(17) Mechanical ventilation	
(18) Increasing FiO_2	
(19) Treatment with indomethacin	
(20) Use of inotropes	
(21) Mild abdominal distension	
(22) Severe abdominal distension	
(23) Bloody stools	
(24) Abdominal tenderness	
(25) Large residuals *(specify volume)*	
(26) Bilious residuals	
(27) Vomiting	
(28) Recent extubation (*specify time)*	
(29) Blood transfusion	
(30) Other *(please specify)*	

Thank you

APPENDIX 3

RETROSPECTIVE REVIEW OF MEDICAL RECORDS – DATASET

DATASET **Baby Data**

General:

- Study ID number
- Mode of delivery
- Gender
- Birth order
- Ethnicity
- Gestation at birth
- Birth Weight
- 5 minute Apgar score
- Age at hospital discharge

Other early / antenatal issues:

- Prolonged rupture of membranes
- Congenital abnormality
- Antenatal steroids
- Timing of first dose of surfactant
- Absent / reversed / reduced end diastolic flow
- Asphyxia
- Intrauterine growth restriction
- Polycythaemia (Hct > 0.7)
- CRIB score (severity of illness)

Overview feeding data:

- Day of first enteral feed
- Volume of first enteral feed
- Type of milk started
- Feeding method (bolus / continuous)
- Day of starting parenteral nutrition
- Day attaining full enteral feeds (150ml/kg/day)

Lines / infection:

- Umbilical arterial catheter (UAC) - insertion and removal
- Umbilical venous catheter (UVC) - insertion and removal
- Percutaneous intravenous central catheter (PICC) - insertion and removal
- Total days on antibiotics

Outcomes:

- Day of diagnosis of necrotising enterocolitis (NEC)
- Bell stage NEC
- Weight at discharge
- Number of days antibiotic treatment for suspected / proven NEC
- Intraventricular hemorrhage (R / L / grade)
- Periventricular leukomalacia

DATASET **Daily data**

Associated illness / severity:

- Hypotension
- Inotropes
- Respiratory support (ventilation / CPAP)
- Increasing oxygen requirement
- Apnoeic / bradycardic episodes
- Acidosis
- Sedation
- Pharmacological paralysis
- Patent ductus arteriosus

Feeding data:

- Volume of enteral feed (ml/day)
- Volume of enteral feed (ml/kg/day)
- Feed interval
- Availability of expressed breast milk
- Type of milk
- Route of feeding
- Use of human milk fortifier
- Use of feed thickener
- Use of Gaviscon
- PN / route of administration of PN

Gut related outcomes:

- Passage of stool
- Use of glycerin suppositories
- Abdominal distension (mild / severe)
- Bloody stool
- Abdominal tenderness
- Abdominal x ray findings
- Presence of Intramural gas on x ray
- Bowel perforation
- Gastric residuals (bilious/ large)
- Feed discontinuation (no. hours)

Drugs:

- Indomethacin / ibuprofen
- Caffeine
- Ranitidine / cimetidine / omeprazole
- Insulin
- Erythromycin
- Other medications

Lines / infection:

- Presence of UVC
- Presence / position of UAC
- Presence of PICC
- Blood culture and result
- CSF culture and result
- Antibiotics given (with or without Metronidazole)

APPENDIX 4

LETTERS OF APPROACH TO CLINICIANS

UK NEONATAL FEEDING SURVEY

Neonatal Unit
Simpson Centre for Reproductive Health
Royal Infirmary of Edinburgh
Little France
Edinburgh
EH16 4SU

Date

Name and address of
Consultant Neonatologist will be inserted here

Dear Dr

I am conducting a UK wide survey of feeding practice in preterm and very low birth weight infants. The Multicentre Research Ethics Committee has approved this proposal. The results from the survey will form the basis of my PhD thesis.

This survey will consist of two parts:

1. A questionnaire to consultant neonatologists aiming to document current opinion and intentions with respect to enteral feeding.
2. A retrospective review of medical records in selected neonatal units to document current feeding practice throughout the United Kingdom.

I invite you to take part by completing the attached questionnaire, which I expect to take approximately 10 – 15 minutes of your time. I enclose an information sheet outlining the background to the study.

Please return the completed questionnaire to me in the stamped addressed envelope provided.

I may contact your hospital unit again with a view to arranging a convenient time to conduct a retrospective review of medical records. Information about this part of the study will be sent separately.

Thank you very much for your help. I hope that a high response rate will allow me to generate high quality observational data that will inform the design of much-needed interventional trials to identify optimum strategies for feeding of vulnerable infants.

Yours sincerely,

Elaine M Boyle MBChB, MD, MSc
Specialist Registrar in Academic Neonatology

UK NEONATAL FEEDING SURVEY

Neonatal Unit
Simpson Centre for Reproductive Health
Royal Infirmary of Edinburgh
Little France
Edinburgh
EH16 4SU

Date

Name and address of consultant neonatologist will be inserted here

Dear

We would like to conduct a survey of feeding practice your neonatal unit, as part of a UK wide survey of feeding in very preterm and low birth weight babies. This will take the form of a retrospective review of medical and nursing records.

Background

It seems, from the published literature and from personal experience, that there is a huge variation in practice in the enteral feeding of very preterm and small infants. A recent small pilot survey of practice in Scotland confirms this and the results have been presented at national and international meetings. Current practice encompasses major differences in the introduction and rate of increase of feeds, the type of feeds given and the time taken to reach full enteral feeds. Serious but conflicting clinical risks accompany the extremes of practice in this area. With fast feed introduction, potential risks are poor gut tolerance of feeds with gastric distension, gastro-oesophageal reflux and aspiration and necrotizing enterocolitis. Conversely, with slow introduction of feeds, risks include regression of gut architecture and integrity, line and gut related sepsis.

Research to date has failed to define the safest and most effective strategies for infant feeding. There is a need for a large randomised controlled trial to answer this question. Before embarking upon such a study, it is essential to document the range of clinical opinion and current practice in order to establish the degree of clinical uncertainty in this area and to determine what strategies would be acceptable to clinicians taking part in an intervention trial.

The Survey

A review of medical records will be carried out to document current feeding practice in infants with birth weight <1500g or <30 weeks gestation admitted to UK neonatal units within a 6 month period.

To maintain confidentiality, all data will be anonymised. Centres and infants will be identifiable only by study number. No comparisons will be made between particular centres. The Multicentre Research Ethics Committee has approved the proposal. Since there will be no local researchers, there will be no requirement for approval from each individual Local Research Ethics Committee though they will be informed about the research. Permission will be sought from the Research and Development Department of your hospital. I enclose a copy of the letter we would send to the trust, with your approval. Appropriate people to be contacted might be the Caldicott Guardian to discuss issues of confidentiality and the Human Resources Department to facilitate arrangements for an outside researcher.

I plan to visit each neonatal unit myself to perform the case note reviews. The development of this survey and results will form the basis of my thesis for the degree of PhD.

I hope that you will agree that this is an important area of research and consider your unit taking part. If you consent to your unit taking part in the survey, I will make arrangements to visit at a mutually convenient time.

I would be grateful if you would return the enclosed form to me or preferably contact me by phone or email, indicating whether you are willing for your unit to be included in the survey and suggesting possible contact names at your hospital.

Thank you for your interest,

Yours sincerely,

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