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Amniotic Fluid and Colostrum as Potential Diets in the Critical Care of Preterm Infants

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Abstract

Amniotic fluid is the enteral "diet" of the developing fetus, while the first mammary gland secretion, colostrum, is the natural diet of the newborn mammal. Both diets contain nutrients but also growth factors, immune-modulating components, and antibacterial agents that support perinatal organ development, particularly of the gastrointestinal (GI) tract. Birth requires a sudden transition to nutrient uptake via the GI tract and exposure to microorganisms. Ingestion of amniotic fluid before birth and of colostrum just after birth helps to adapt GI functions and provides protection against detrimental immune responses. Experimental studies indicate that these fluids may also have beneficial effects in certain GI disease conditions, particularly those related to immature digestive and immune function. We provide a brief review of the functions and composition of mammalian amniotic fluid and colostrum, and we describe how these fluids may have a therapeutic potential for GI conditions in some pediatric patients, particularly preterm infants. The composition of the two fluids varies widely among different species and the effects are likely highly species specific. Some effects may however be species independent, maybe allowing colostrum from one species (i.e., lactating cows) to be used as the first enteral diet for infants for whom mother's milk is lacking. The use of amniotic fluid and bovine colostrum in the critical care of neonates is still at an experimental stage, but animal studies have shown promising results.

List of Abbreviations

GI Gastrointestinal
MEN Minimal enteral nutrition
NEC Necrotizing enterocolitis
SBS Short bowel syndrome

Introduction

Nutrition is an important contributor to the growth and development of infants, both healthy and infants born with or who develop complications. This chapter will address the role of some alternative diets, amniotic fluid and bovine colostrum, for infants that are sensitive to develop conditions that compromise the function of the gastrointestinal (GI) tract, such as necrotizing enterocolitis (NEC). NEC is primarily seen in preterm infants born prior to 36 weeks gestation and is a leading cause of mortality in preterm infants in neonatal intensive care units (Henry and

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Moss 2009; Berman and Moss 2011). This disease sometimes requires intestinal resection that subsequently leads to the development of short bowel syndrome (SBS) (Aunsholt et al. 2014). Research in this sensitive patient population is difficult, and in vivo and in vitro models may be used to determine the optimal nutritional strategy in relation to the type of diet, nutritional supplements, and feeding route and volume for infants at risk of NEC and SBS. Mother's milk is the natural and optimal diet for infants to support their nutritional demands. Nevertheless, alternatives need to be considered, because mother's milk is not always available in adequate amounts, if at all. Amniotic fluid and colostrum are of interest as alternative diets in this context because these fluids represent the natural diets that the developing mammal is exposed to from the transition from parenteral nutrition before birth to enteral nutrition after birth (Fig. 1).

Infants are born with an immature GI tract and a competent but naïve immune system that is being matured by feeding and exposure to external stimuli, including bacteria. For preterm infants, the GI tract and immune system are even more naïve and immature. The exact etiology of NEC is unknown, but prematurity is a central risk factor, and thus these infants are at high risk of developing NEC. Other contributing risk factors are enteral feeding with infant formula and an inappropriate composition and density of the GI microbiota. As mentioned, NEC may lead to SBS, but this condition can also be a consequence of congenital defects or other complications that need removal of a part of the small intestine. As this may cause malabsorption and consequently malnutrition, intestinal adaptation to SBS is crucial for the absorption of nutrients and fluids (Aunsholt et al. 2014). For both NEC and SBS patients, feeding with the right diet, in the appropriate amounts and at the right time, may be crucial to improve maturation and for the intestinal environment to become less sensitive to nutritional and microbial insults.

The mother's own milk is recommended as the sole diet for infants under the age of 6 months (WHO 2010). This is because it is believed to contain the appropriate contents of nutrients for growth and development of the infant. However, the milk not only serves as a source of growth for the newborn but also supplies bioactive factors that assist in the maturational process of the GI tract and immune system, including induction of tolerance and provision of passive immunity against

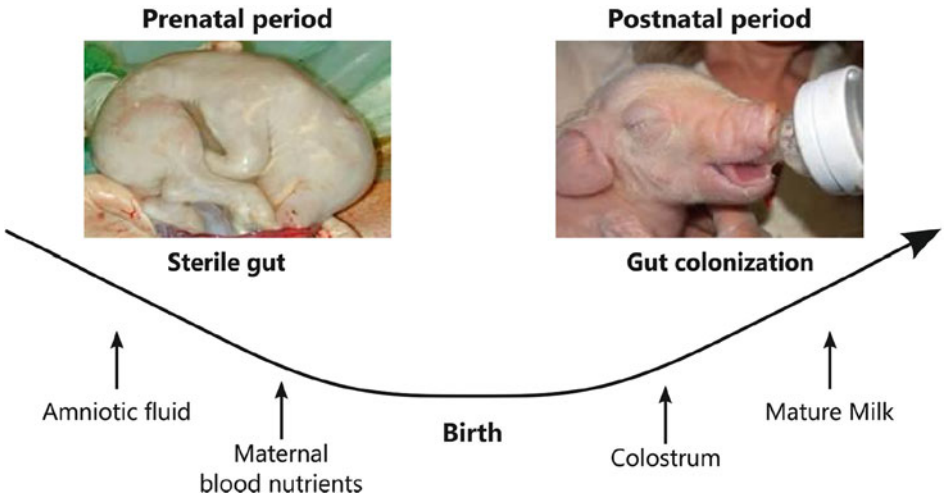

Fig. 1 Nutritional transition at birth. During fetal development in mammals, nutrient uptake occurs mainly through the parenteral route. The fetus is provided with nutrients via the maternal blood supply through the umbilical cord. The fetus also swallows considerable amounts of amniotic fluid that stimulates somatic and gastrointestinal growth. At birth, the route of nutrient uptake changes from parenteral to enteral with the first uptake of milk. Enteral intake of nutrients, in combination with bacterial colonization, stimulates maturation of the newborn digestive system

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Table 1 An overview of some bioactive factors in amniotic fluid and colostrum, grouped according to their antimicrobial, immune regulating, or growth factor functions. The amount of each bioactive factor in each of the two fluids vary among different species and different stages of pregnancy (amniotic fluid) and lactation (colostrum) (Brandtzaeg 2003; Calhoun 2002; Caplan et al. 2001; Espinoza et al. 2002, 2003; Field 2005; Good et al. 2012; Hurley and Theil 2011; Kerr 1990; Lu et al. 2007; Pakkanen and Aalto 1997; Wagner et al. 2008; Walker 2010; Yoshio et al. 2003)

Antimicrobial factors	Immune factors	Growth factors
Bactericidal/permeability-increasing protein	Cytokines	Epidermal growth factor
Calprotectin	Fatty acids	Erythropoietin
Cathelicidin	Growth factors	Fibroblast growth factor
Defensins (α and β)	Hormones	Granulocyte colony-stimulating factor and hepatocyte growth factor
Fatty acids		Insulin-like growth factor
Immunoglobulins		Transforming growth factor β1 and β2
Lactoferrin		
Lactoperoxidase		
Lipopolysaccharide-binding protein		
Lysozyme		
Oligosaccharides/glycoconjugates		

infections (Bernt and Walker 1999; Playford et al. 2000; Brandtzaeg 2003; Field 2005; Walker 2010). The bioactive factors in amniotic fluid and colostrum (Table 1) include antimicrobial, immune-stimulating, and growth factors that may be important for reducing the risk of developmental deficits, including those leading to NEC. Mother's milk is often absent or limited in the first days after preterm birth (Schanler et al. 2005). The infants may therefore receive infant formula, which lacks these essential bioactive factors. A study in preterm infants comparing preterm infants exclusively on the mother's own milk or the mother's own milk supplemented with human donor milk showed that the amount of maternal milk was inversely correlated to NEC (Montjaux-Régis et al. 2011), while a Cochrane review has concluded that infant formula increases the risk of NEC in preterm infants compared with donor breast milk (Quigley et al. 2008). In preterm pigs, bovine colostrum is protective against NEC with similar efficacy as human donor milk (Jensen et al. 2013). The optimal nutritional strategy may be minimal enteral nutrition (MEN) that combines small doses of enteral nutrition with parenteral nutrition. This provides the infant with adequate intake of nutrients through the parenteral nutrition but still provides the beneficial effects of enteral nutrition on intestinal and immune system maturation, especially in preterm infants for whom it is impossible to give the mother's own milk or donor breast milk. The administration of colostrum in slowly advancing volumes, directly after birth and during the transition from parenteral to enteral nutrition, has proven to protect against NEC in preterm pigs (Cilieborg et al. 2011). In contrast, the effect of MEN in preterm infants remains uncertain (Morgan et al. 2011; Fallon et al. 2012). Most studies in infants have not clearly defined the effects of diet type on NEC, as the enteral diet has often been a mixture of the mother's own milk, donor human milk, and/or infant formulas based on bovine milk products.

Alternative sources of the first enteral diet, when mother's milk is not an option, need to be identified. This is important for GI maturation and protection but clearly also for nutrient uptake and body growth, as well as maintenance of basic physiological parameters such as fluid homeostasis. Such alternative sources of the first diet may include amniotic fluid and the first milk, colostrum, potentially from another species, such as the cow. For amniotic fluid, the potential to use this as a supplementary enteral diet after birth is mainly targeted toward feeding the infant its own amniotic fluid collected during the birth process (e.g., at preterm cesarean section). This would be a way to

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continue feeding the enteral diet that the fetus was ingesting already before birth and that may have a particularly important role for the immature GI tract. Colostrum contains a large number of bioactive factors, which may aid in GI growth, maturation, priming of the immune system, and the succession of a beneficial microbiota in the newborn infant (Bernt and Walker 1999; Playford et al. 2000; Field 2005; Sangild et al. 2006; Walker 2010). We acknowledge that the concepts of feeding the mother's amniotic fluid or bovine colostrum just after preterm birth are only experimental at this stage. However, there is the potential that these fluids might be seen as novel sources of protective enteral diets in the critical care of neonates during the difficult transition from parenteral nutrition to enteral nutrition (Fig. 1).

Amniotic Fluid

Amniotic fluid is essential for fetal survival and development throughout gestation. It protects the fetus against mechanical injury and physical stressors but also upholds fetal homeostasis through recirculation of fetal secretions and maintenance of amnion integrity and protects against and eradicates infections (Harman 2008). In addition, amniotic fluid is a source of enteral nutrition for the developing fetus, thereby providing 10–15 % of fetal energy and nitrogen requirements in addition to the nutrients provided by maternal blood across the placenta via the umbilical cord (Pitkin and Reynolds 1975; Tisi et al. 2004).

From mid-gestation, amniotic fluid is primarily a product of fetal urine excretion, while fetal swallowing is the principal route of amniotic fluid removal (Ross and Brace 2001). The fetus ingests an amniotic fluid volume equivalent to 5–10 % of the body weight but may swallow as much as 15–20 % or up to 800 ml per day in the late fetal period (Pritchard 1966; Sherman et al. 1990). Fetal swallowing of amniotic fluid also affects fetal somatic and GI growth. This is evident from observations in neonates born with congenital intestinal atresia and reduced birth weight as a result (Blakelock et al. 1998; Condino et al. 2004; Schaart et al. 2006; Burjonrappa et al. 2010). Furthermore, esophageal ligation studies in pigs (Sangild et al. 2002), rabbits (Mulvihill et al. 1985; Buchmiller et al. 1993; Cellini et al. 2006), and sheep (Trahair et al. 1986; Trahair and Harding 1995; Trahair and Sangild 2000) demonstrate reduced somatic and GI growth in late gestation when amniotic fluid swallowing is obstructed. Interestingly, the effects of esophageal ligation are reversed by infusion of amniotic fluid (Trahair and Sangild 2000) or reconstruction of fetal swallowing (Trahair and Harding 1995).

Amniotic fluid contains electrolytes, lipids, proteins, amino acids and peptides, lactate, enzymes, and hormones (Underwood et al. 2005). The protein fraction has been studied most extensively and has been found to contain a range of low-weight proteins with potent bioactivities including growth factors, cytokines, and antimicrobial peptides (Table 1). The concentration of bioactive proteins in amniotic fluid varies greatly between individuals and gestational ages and changes in response to conditions such as intrauterine infections (Bastek et al. 2011). Amniotic fluid stimulates proliferation of gastric (Mulvihill et al. 1989; Kong et al. 1998) and intestinal epithelial cells (Hirai et al. 2002), probably via its content of growth factors. These include epidermal, fibroblast, hepatocyte, insulin-like, and transforming growth factors (Wagner et al. 2008) as well as hematopoietic growth factors including erythropoietin and granulocyte colony-stimulating factor (Calhoun 2002). Amniotic fluid also possesses immunosuppressive properties, as demonstrated by in vitro cell studies. Amniotic fluid from different mammalian species attenuates induced inflammatory responses and activation of intestinal epithelial cells (Good et al. 2012), dendritic cells (Møller et al. 2011a), macrophages (Lang and Searle 1994; Maheshwari et al. 2011), and lymphocytes (Shohat and Faktor 1988). The

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immunomodulatory effects may to some degree be ascribed to transforming growth factor β1 and β2 (Lang and Searle 1994; Claud et al. 2003; Rautava et al. 2010; Maheshwari et al. 2011; Rautava et al. 2012) and epidermal growth factor (Good et al. 2012). Antimicrobial effects of amniotic fluid have also been demonstrated in vitro (Yoshio et al. 2003) and associated with the content of antimicrobial peptides, such as α-defensin and cathelicidin, and lysozyme (Yoshio et al. 2003), bactericidal/permeability-increasing protein, calprotectin (Espinoza et al. 2003), and lipopolysaccharide-binding protein (Espinoza et al. 2002). In addition to the molecular bioactive constituents, amniotic fluid also contains a heterogeneous population of cells including a subpopulation of easily cultivable pluripotent stem cells (Shaw et al. 2011). The origin of these stem cells and their function in fetal development remain uncertain. They may originate from a unique cell mass that differentiates into diverse progenitors at different stages of embryonic development, enters the amniotic cavity, migrates through to the amniotic fluid, and implants into specific tissues (Tong 2013).

It has been suggested to use amniotic fluid as MEN or an immunomodulatory supplement to infant formula during the first days after preterm birth when human milk is not available (Calhoun 2002). The use of "simulated amniotic fluid," consisting of sterile, isotonic electrolyte solution with hematopoietic growth factors, was tested in preterm infants prior to initiation of enteral feeding (Sullivan et al. 2002; Christensen et al. 2005) and in term neonates (Barney et al. 2007) and during a period of bowel rest in the recovery after NEC-related surgery (Lima-Rogel et al. 2003). In these small trials, it was demonstrated that this "simulated amniotic fluid" was well tolerated at doses of up to 20 ml/kg/day and tended to improve tolerance to enteral feeding.

Colostrum

Colostrum is the first milk produced after a mammal has given birth, and it gradually changes its special composition to that of mature milk shortly after birth. In humans, the colostrum is produced mainly during the first 5 days after birth with the composition gradually changing to that of mature milk during the first 2 weeks after birth (Prentice 1995; Murtaugh et al. 2005). Bovine colostrum is produced mainly during the first 2 days after parturition (Blumand Hammon 2000; Playford et al. 2000). Like milk, colostrum contains proteins, carbohydrates, lipids, vitamins, minerals, electrolytes, and trace minerals. Furthermore, colostrum contains large amounts of bioactive factors (Table 1) like growth factors, cytokines, and antimicrobial peptides, in addition to the presence of bacteria and cells (Committee on Nutritional Status During Pregnancy and Lactation and Institute of Medicine 1991; Playford et al. 2000; Field. 2005; Cabrera-Rubio et al. 2012). The major whey protein group in bovine colostrum, immunoglobulins, is responsible for immune exclusion by agglutination of microbes and neutralization of pathogens and bacterial enterotoxins (Kerr 1990; Brandtzaeg 2003; Hurley and Theil 2011). Immunoglobulin A dominates in human colostrum, while the primary immunoglobulin in bovine colostrum is immunoglobulin G. Other bioactive factors in the protein fraction of bovine colostrum include antimicrobial factors. Lactoferrin is able to assist the host's innate defense against microbes and their toxins and acts in synergy with the antibacterial enzyme lactoperoxidase, which together with lysozyme is involved in the antimicrobial defense (Pakkanen and Aalto 1997). Bioactive factors are also found in the other nutrient classes in colostrum. In human colostrum, oligosaccharides and glycoconjugates in the carbohydrate fraction act as prebiotics that stimulate the succession of a beneficial microbiota in the colon (Walker 2010). In contrast, the level of oligosaccharides in bovine milk is very low (Gopal and Gill 2000). Long-chain polyunsaturated fatty acids are also present in high amounts in colostrum and have shown to

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reduce the incidence of NEC and intestinal inflammation in a neonatal rat model of NEC (Caplan et al. 2001; Lu et al. 2007).

To have physiological relevance, the colostrum bioactive factors have to pass through the GI tract to the site of action without being degraded. To facilitate this, bovine colostrum contains glycoproteins and protease inhibitors (inhibiting trypsin, chymotrypsin, and elastase), and furthermore, some factors are hard to digest by being acid resistant (Lindberg 1979; Thapa 2005). Some colostrum bioactive factors are activated during the digestion in the GI tract (Shah 2000; Liepke et al. 2002; Silva and Malcata 2005). Thus, bioactive factors have to be present in sufficient quantity, in an active state, and not being inhibited by other factors to be able to exert their effects on the intestinal environment (Bernt and Walker 1999). In both children and adults with SBS, supplementation with bovine colostrum is well tolerated although the effects on intestinal function, compared with a mixed milk diet, were minimal (Lund et al. 2012; Aunsholt et al. 2014).

Applications of Amniotic Fluid in the Critical Care of Preterm Neonates

Studies have been conducted to investigate the NEC-protective effects of postnatal feeding with amniotic fluid in both preterm pigs and young mice (Table 2). The typical experimental design to investigate the effects of amniotic fluid and colostrum products on NEC development in preterm pigs is shown in Fig. 2. In these experiments, amniotic fluid was given as MEN, as a bioactive supplement to enteral formula feeding, or both. Siggers et al. (2013) found that amniotic fluid reduced the incidence of NEC in preterm pigs when fed both as MEN and as part of the later full enteral feeding with infant milk formula. Compared with porcine colostrum, which completely prevented NEC, amniotic fluid was less efficacious as indicated by the lacking effect on brush-border enzyme activities. Nevertheless, postnatal feeding with amniotic fluid affected the intestinal expression of many genes involved in innate immune system and inflammatory pathways. Similarly, the administration of amniotic fluid to a 10-day-old mice reduced NEC severity scores, probably via immunomodulatory effects of epidermal growth factor (Good et al. 2012). Further studies in the preterm pig model showed no effects of amniotic fluid on NEC incidence or severity when the fluid was fed exclusively as MEN during a 2-day period of parenteral nutrition (Østergaard et al. 2013) or

Table 2 Overview of studies in preterm pigs and young mice testing the effect of amniotic fluid (AF) on necrotizing enterocolitis (NEC). In all studies, infant formula was used as control diet

Study	Study aims	Outcome
(Good et al. 2012)	Test NEC-protective effects of murine AF given to postnatal full-term mice	Murine AF reduces NEC severity via regulation of EGF receptor and TLR-4
(Siggers et al. 2013)	Experiment 1: Test efficacy of porcine AF used as MEN diet + mixed into formula feeding	Results: Reduced NEC after AF in formula; inflammation/microbiota changes
	Experiment 2: Test efficacy of porcine AF mixed into formula feeds	Results: No effects of AF on NEC or gut structure or functions
(Østergaard et al. 2013)	Experiment 1: Test effect of porcine/human AF used as MEN in pigs	Results: Increased body growth, reduced gut cytokines
	Experiment 2: Test effects of porcine/human AF used as MEN in pigs, followed by formula feeding	Results: Increased body growth and no (pAF) or negative (hAF) effects on NEC

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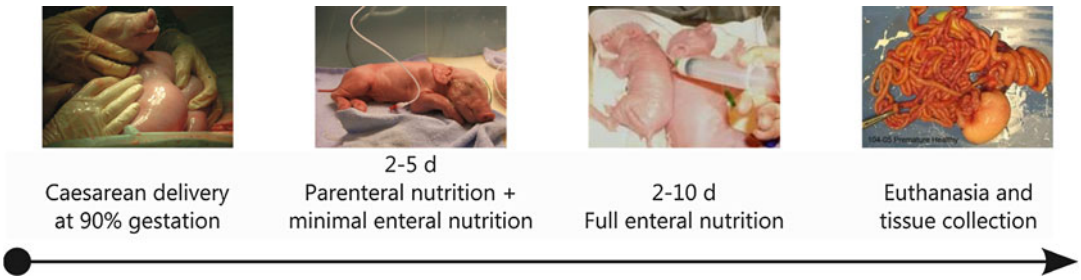

Fig. 2 Protocol for experimental clinical nutrition experiments in preterm pigs. Preterm pigs are delivered by cesarean section at 90 % of gestation and stabilized in incubators that are heated and oxygenized. Piglets are then provided with parenteral nutrition for 2–5 days, which may be supplemented with minimal enteral nutrition (i.e., small boluses of enteral nutrition), followed by a transition to full enteral feeding. The enteral nutrition provided may be amniotic fluid, colostrum or mature milk from various species, or various infant milk formulas

exclusively as a supplement to full enteral formula feeding introduced after a 2-day period of total parenteral nutrition (Siggers et al. 2013). Amniotic fluid provision during the first days after birth induced small but consistent increases in body weight gain, but whether this resulted from increased fluid retention or increased dry mass or both remains to be resolved. Finally, intraperitoneal injection of amniotic fluid stem cells is well tolerated in neonatal rats (Ghionzoli et al. 2010) and prevents NEC (Zani et al. 2014). Together, these studies indicate that the postnatal administration of amniotic fluid and amniotic fluid stem cells to preterm neonates does not improve GI function per se but may modulate intestinal inflammatory responses and cytokine production. Future studies will demonstrate whether this may reduce the sensitivity to NEC during the critical transition from parenteral to enteral feeding.

Applications of Bovine Colostrum in the Critical Care of Preterm Neonates

Bovine colostrum has in studies in a preterm pig model of NEC (Fig. 2) shown promising results for the future use of bovine colostrum for preterm infants, as bovine colostrum repeatedly has been shown to be better than infant formula in improving GI function and resistance against NEC (Table 3). In one study (Bjornvad et al. 2008), the investigators compared bovine colostrum, porcine colostrum, and infant formula in preterm pigs to investigate whether the protective effects of colostrum were species specific. This study showed that NEC severity was lower in both groups of pigs fed colostrum, compared with pigs receiving infant formula. Furthermore, formula feeding resulted in decreased villus height and nutrient digestive capacity, while it increased luminal lactic acid levels compared with both colostrum diets which were similar for the majority of the measured intestinal parameters. This study suggests that the protective effect of colostrum is at least partly species independent. This is further supported by the finding that both bovine colostrum and human donor milk reduce NEC lesions and proinflammatory cytokines and increase nutrient absorption and body weight gain, relative to formula (Jensen et al. 2013). Another study investigated how milk after different stages of lactation influenced gut responses (Li et al. 2014). The study showed that bovine colostrum was moderately superior to mature bovine milk as observed by improved mucosal weight, villus height, and nutrient digestive capacity, while gut permeability, nutrient fermentation, and NEC severity were decreased. In this study, both milk products improved gut responses compared with infant formula. Bovine colostrum also increases mucosal growth with a concomitant increase in first-pass splanchnic threonine utilization, protein synthesis, and mucin synthesis in the distal small

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Table 3 Overview of studies in preterm pigs testing the effect of different enteral diet interventions on the incidence of NEC. In all studies, infant formula was used as control diet

Study	Study aims	Outcome
(Bjornvad et al. 2008)	Test the species specificity of bovine and porcine colostrum	Colostrum had a species-independent improvement on gut maturation and reduced NEC incidence
(Cilieborg et al. 2011)	Test the efficacy of bovine colostrum as MEN diet	Colostrum MEN improved NEC resistance and intestinal structure and function
(Jensen et al. 2013)	Test species specificity of bovine colostrum and human donor milk	Bovine colostrum and human donor milk show improved NEC protection and gut structure and function, relative to infant formula
(Li et al. 2014)	Test if mature bovine milk had less bioactivity than bovine colostrum	Gut maturational effects improved by milk and especially colostrum, relative to formula
(Møller et al. 2011b)	Compare bovine colostrum with formula enriched with gangliosides and sialic acids	Improved NEC resistance and gut structure and function of colostrum versus formula. No effects of formula enrichments
(Puiman et al. 2011)	Test if colostrum improves mucosal growth, protein synthesis, and mucin synthesis	Bovine colostrum increased intestinal threonine metabolism, gut barrier function, and mucin synthesis
(Støy et al. 2013)	Investigate if bovine colostrum may restore intestinal damage after exposure to formula feeding	Bovine colostrum restored intestinal function and structure

intestine(Puiman et al. 2011). Thus, colostrum feeding may lead to increased intestinal threonine metabolism and subsequently improved gut barrier function that may support NEC resistance. Bovine colostrum may also restore the mucosa after an initial inflammatory insult by feeding infant formula to preterm neonates. Just 8 h of formula feeding is enough to initiate such inflammatory responses in the preterm pig intestine (Siggers et al. 2011). In preterm pigs fed formula for such a short time span, subsequent feeding with bovine colostrum reduces the NEC severity and interleukin-1 beta and interleukin-8 concentrations and increases villus height and digestive functions, relative to pigs continuously fed with infant formula (Støy et al. 2013).

Bioactive factors in colostrum may be responsible for the beneficial effects of bovine colostrum on the intestine in preterm neonates, although it has been difficult to demonstrate beneficial effects of adding milk bioactives, such as gangliosides and sialic acid to formula-fed preterm pigs. (Møller et al. 2011b) Only bovine colostrum improved NEC resistance and intestinal structure and function compared with control formula. Thus, the beneficial effects of colostrum may result from a combined, synergistic effect of many bioactive factors (Chatterton et al. 2013).

Based on studies in preterm pigs, the most NEC-preventive feeding regimen is when bovine colostrum is given as MEN during the first days after birth (16–30 mL/kg/day) and reaches about 120 mL/kg/day on day 5 (Cilieborg et al. 2011). Similar MEN feeding regimen, using infant formula, did not prevent NEC or improve mucosal structure and function, relative to an abrupt transition to formula after a period of parenteral nutrition. Only MEN feeding with colostrum resulted in reduced bacterial load and organic acid concentration, thereby reducing the abundance of total bacteria in the distal small intestine.

There are a series of safety concerns that need to be carefully addressed before bovine colostrum can be tested in preterm infants that have no access to mother's milk. First, it should be noted that in many of the above preterm piglet studies, there has been a tendency to observe a greater frequency of lesions in the stomach region when feeding high amounts (e.g., 120 mL/kg/day) of bovine colostrum (Li et al. 2014; Støy et al. 2013). Also the use of bovine colostrum as the sole enteral diet after the first week of life may not be advantageous. While it is beneficial for preterm infants that bovine

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colostrum contains a large amount of digestible protein (of which the major fraction is immunoglobulin G in the whey fraction), there may be a concern that preterm infants will receive excess amounts of protein when fed enterally with too much bovine colostrum. Finally, there are also possible allergic reactions to cow milk proteins in infants. Despite these reservations, the preterm pig studies would suggest that bovine colostrum, fed as MEN (e.g., 10–50 mL/kg/day) over the first days after birth, may be of benefit for the immature GI tract in preterm neonates.

Guidelines and Protocols

The above animal studies suggest that there is a potential to use amniotic fluid and bovine colostrum as MEN diets in the immediate postnatal period of preterm infants, if mother's milk is not available. Amniotic fluid is much less investigated than bovine colostrum, but studies in pigs using 40–80 mL/kg/day for the first 2–5 days after birth (Fig. 2) suggest that amniotic fluid could have beneficial effects to support the later transition to full enteral feeding with milk diets. Preliminary results suggest that amniotic fluid collected from another species is not efficacious, at least not in pigs, or may even be detrimental.

The animal experimental data are clearer for the use of bovine colostrum as MEN feeding than for amniotic fluid. Preterm pig studies consistently show that bovine colostrum, provided in moderate amounts during the initial week after preterm birth (20–120 mL/kg/day), has markedly better effects on growth and development than any formula tested until now. On the other hand, it appears that colostrum may not be advantageous for more long-term use and when provided in larger volumes. This leads us to suggest that bovine colostrum should be used only as MEN for preterm infants, providing 10–50 mL/kg/day over the first 5–10 days of postnatal life, until mother's milk or an alternative diet is available.

Applications to Other Complications

As indicated above, the possible use of amniotic fluid as a critical care diet for preterm infants requires further study in animal models before human studies are justified. Possibly, amniotic fluid collected from pregnant mothers at the time of a preterm cesarean section, and fed to her own preterm infant, is the first way to test this novel feeding strategy. There are a series of practical complications and microbiological safety concerns, especially when the preterm delivery is associated with maternal infection. The concentration of bioactive proteins in amniotic fluid is also affected during intrauterine infections (Bastek et al. 2011), and it is clearly important not to provide amniotic fluid that is bacterially contaminated. However, amniotic fluid is the enteral diet that the preterm delivered newborn was drinking before birth, and intuitively and physiologically, this may exactly be what is required to support the immature intestine to adapt to enteral feeding and bacterial colonization. It cannot be excluded that human amniotic fluid or even amniotic fluid from another species could be relevant as an enteral diet for clinical conditions other than preterm birth, but first, its efficacy for preterm infants or other compromised newborn infants must be documented.

For the use of colostrum in clinical care, even colostrum from cows, the case is different. Pilot studies in older human preterm infants and adults suffering from SBS suggest that bovine colostrum is well tolerated (Lund et al. 2012), and studies in preterm infants are being planned. Regardless, there are many questions remaining regarding the optimal time, dosage, and duration of the feeding.

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In addition, it will be a large task to secure the product stability and microbiological safety for such a new diet for use in the pediatric ICU.

Careful considerations regarding species specificity are required for colostrum (bovine, pig, human) and in relation to interpretation of results from animal models. For bovine colostrum, the contents of immunoglobulin G and many other components are much higher than in humans, and whether this constitutes an advantage or a possible risk is yet unknown. For both amniotic fluid and bovine colostrum, it is important to note that the amount of nutrients fluctuate over time and vary within and between species (Murtaugh et al. 2005; Bastek et al. 2011). The fluctuation of nutrients and bioactive factors underlines that the neonates have specific needs at a certain time point and that the needs differ between species. This should be considered when formulating nutritional products to human infants based on bovine colostrum. However, the unique composition with a high content of bioactive factors may benefit the neonates unable to receive their own mother's colostrum and milk. Studies are testing the use of bovine colostrum for pediatric patients subjected to chemotherapy, and these studies are based also on model studies in piglets (Pontoppidan et al. 2014). While the use of bovine colostrum in intensive care patients is new, the product has been extensively used over many years in healthy adults, especially in sports medicine and human exercise and fitness (Rathe et al. 2014).

Processing procedures may be required for these alternative diets since the bacterial contamination standards are set at a very low level for infant formula or donor breast milk given to preterm infant (Ewaschuk et al. 2011). A prerequisite for the use of amniotic fluid and bovine colostrum in a clinical setting is that a product with low bacterial contamination and which is easy to handle and store can be produced. Several processing methods, for example, spray drying, gamma irradiation, and pasteurization, can be employed to increase storage time, to reduce bacterial load, and to facilitate handling of the products. However, the bioactivity of bovine colostrum also needs to be preserved, leaving the number of feasible methods limited. A study in preterm pigs has shown that bovine colostrum maintains the beneficial effects on the preterm pig intestine after spray drying, gamma irradiation, and pasteurization (Støy et al. 2013, unpublished data). This is supported by the aforementioned study by Li et al. (2014) documenting that homogenization, pasteurization, and spray drying of milk to whole milk powder are not as detrimental to gut responses as the milk processing performed during infant formula production, including modification of milk fractions. Whole milk powder induced in general the same beneficial effects as mature breast milk on the GI environment and thus was markedly better that infant formula.

Conclusion

Amniotic fluid and bovine colostrum could potentially serve as alternative diets either to protect infants against intestinal inflammation and injury or for infants already suffering from intestinal inflammation and injury such as NEC and SBS. The safety and efficacy of amniotic fluid and bovine colostrum still needs to be better investigated in both experimental studies and clinical trials.

Summary Points

- Mother's milk is the natural diet for infants to support their nutritional demands, but mother's milk is not always available for preterm infants in adequate amounts, if at all. Thus, alternatives need to be considered.

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- Amniotic fluid and bovine colostrum contain bioactive factors that support perinatal organ growth and development in mammals.
- Animal studies indicate that amniotic fluid and bovine colostrum protect against necrotizing enterocolitis.
- The composition of amniotic fluid and colostrum varies widely among different species, and the beneficial effects are likely highly species specific although some differences may be also species independent.
- Pilot trials should be initiated to investigate the efficacy and safety of providing amniotic fluid or bovine colostrum in the critical care of human neonates.

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