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POTENTIAL EFFECTS OF BOVINE COLOSTRUM IN PREVENTION OF NECROTIZING ENTEROCOLITIS: A REVIEW

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ABSTRACT

Objectives: Necrotizing enterocolitis is a critical gastrointestinal disorder predominantly affecting neonates. Bovine colostrum is a nutrient-dense first secretion from cows postpartum. Bovine colostrum is abundant in immunoglobulins, antimicrobial peptides as well as growth factors, making it a promising candidate for nutritional intervention for necrotizing enterocolitis. This review aims to critically assess the existing preclinical and clinical evidence on the efficacy of bovine colostrum supplementation in reducing the incidence and severity of necrotizing enterocolitis in neonatal populations.
Methods: A literature search was conducted using PubMed and Scopus databases. Relevant animal trials and human randomized controlled trials evaluating the impact of bovine colostrum on necrotizing enterocolitis incidence and severity were analysed.
Key findings: Preclinical studies in neonatal piglet models consistently demonstrate that bovine colostrum reduced the incidence and severity of necrotizing enterocolitis compared to infant formula, with mechanisms involving enhanced gut barrier integrity, microbiota modulation and reduction in inflammation. Bovine colostrum outcomes were often comparable or superior to human donor milk. However, recent randomised controlled trials in preterm human infants have not shown a statistically significant reductions in necrotizing enterocolitis incidences with bovine colostrum supplementation, possibly due to differences in product processing, dosage and open-label study designs.
Conclusions: Despite promising outcomes in zootechnical models, current clinical evidence does not confirm efficacy of bovine colostrum in necrotizing enterocolitis prevention in human neonates. Further high-quality, standardized, double-blinded clinical trials are needed to clarify its potential in infant care.

KEYWORDS

Preterm Infants, Neonatal Nutrition, Gut Microbiota, Infant Formula, Cow's Milk

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Introduction.

Bovine Colostrum (BC) is the first secretion from the mammary gland of a cow that is produced in the first 24 to 72 hours after the birth of a calf. In contrary to mature milk, BC is not designed to meet the long-term nutritional needs but rather to be a short-term, immediate and intense immunological and nutritional support for a newborn calf. Its complex biochemical buildup includes the macronutrients (proteins, carbohydrates and fats), micronutrients (vitamins, minerals) and a rich array of bioactive compounds that have protective, anabolic and regulatory functions (Stelwagen et al. 2009). BC's molecular abundance explains the increasing interest of researchers and physicians in BC as a therapeutic and nutritional agent in human neonatology, especially in the context of preterm infant care and prevention of necrotizing enterocolitis (NEC).

One of the most characteristic qualities of BC is its extremely high immunoglobulin concentration, which contributes a major part of the overall protein content. The dominating fraction is the immunoglobulin G (IgG), which constitutes for almost 86% of all of the immunoglobulins. In BC the IgG concentration can reach up to 50.5 mg/mL - more than 1000 times more than in human colostrum, which has IgG concentration of only 0.43 mg/mL (Kessler et al. 2020). This difference is evolutionary driven - ruminants do not exhibit significant transport of immunoglobulins through the placenta, so the calves are entirely dependent on the colostrum when it comes to passive immunity (Lopez et al. 2022). IgG present in BC has ability to bind a wide range of pathogens including *Escherichia coli*, *Salmonella spp*., *Rotavirus* and *Cryptosporidium parvum*, providing mucosal immunity until neonate's own immune system is mature enough to fight off pathogens. Those functions could potentially translate into human neonates, whose mucosal immunity is also immature in the time following birth (Torow et al. 2023)

In addition to immunoglobulins, bovine colostrum is exceptionally rich in components of innate immunity. As noted by Stelwagen et al. (2009), it contains a number of cytokines (e.g., IL-1β, IL-6, TNF-α), chemokines, acute phase proteins and soluble receptors such as soluble CD14. These molecules play a key role in coordinating the infant's immune response, modulating inflammatory processes and promoting tolerance to commensal intestinal microflora. Cytokines present in colostrum can stimulate local activation and proliferation of immune cells within the gut-associated lymphoid tissue (GALT), which is essential for the maturation of mucosal immunity in newborns. In addition, soluble cytokine receptors and their antagonists are involved in regulating the immune response by neutralizing pro-inflammatory signals, which may reduce the risk of uncontrolled inflammation.

Bovine colostrum is also a rich source of antimicrobial peptides and enzymes, such as lactoferrin, lysozyme, lactoperoxidase and β-defensins (Stelwagen et al. 2009). These proteins act synergistically to inhibit bacterial adhesion to the epithelium, neutralize endotoxins and maintain the integrity of the intestinal barrier. For example, lactoferrin exhibits antimicrobial activity not only by binding free iron necessary for bacterial growth, but also by damaging microbial membranes and modulating the host immune response (Wang et al. 2019). Lactoferrin has been shown to reduce intestinal inflammation and promote intestinal colonization by bifidobacteria in newborns. Lysozyme enzymatically degrades the peptidoglycan layers of Gram-positive bacteria, while lactoperoxidase, through the thiocyanate/hydrogen peroxide system, inhibits microbial metabolism and proliferation. These mechanisms are particularly important during the early colonization of the gastrointestinal tract, when excessive proliferation of pathogens can cause inflammatory reactions and tissue damage.

From a nutritional standpoint, colostrum significantly outperforms mature milk in almost every category. It contains higher levels of total protein (14.0% vs. 3.1%), fat (6.7% vs. 3.7%) and total dry matter (23.9% vs. 12.9%), reflecting its role as a concentrated energy source. In addition, colostrum provides higher amounts of fat-soluble vitamins (A, D, E, K) and B vitamins, including B12 and folic acid. Key minerals - such as calcium, phosphorus, magnesium and zinc - are present in bioavailable forms, supporting skeletal development, enzymatic activity and immune competence (Stelwagen et al. 2008, Playford et al. 2021).

The unique composition of bovine colostrum makes it an extremely valuable source of nutrients and immune components for newborn calves. The wealth of bioactive compounds contained in colostrum not only meets the health needs of the neonates, but also contributes to long-term growth and development. In addition, due to its antimicrobial and immune system modulating properties, bovine colostrum is being considered as a promising supplement for human infant nutrition. Table 1 presents the most important components of bovine colostrum as well as their functions.

Table 1. Bioactive components of bovine colostrum and their biological functions (from Stelwagen et al. 2008)

Component group	Examples	Biological function
Macronutrients	Proteins, fats, carbohydrates	Provide energy and structural components
Specific proteins	Casein, albumins, α-lactalbumin	Nutritional, transport functions
Vitamins	A, D, E, K; B1, B2, B6, B12, folate	Antioxidation, metabolism, development
Minerals	Calcium, phosphorus, zinc, magnesium, iron	Bone mineralization, enzymatic and immune functions
Immunoglobulins	IgG, IgA, IgM	Passive immunity, pathogen neutralization

Cytokines and chemokines	IL-1β, IL-6, TNF-α, TGF-β, interferons	Regulation of immune response
Antimicrobial peptides	Lactoferrin, lysozyme, lactoperoxidase, β-defensins	Antibacterial activity, microbiota modulation
Growth factors	IGF-I, IGF-II, EGF, TGF-β, PDGF	Epithelial development, tissue repair, gut maturation
Oligosaccharides	Lactose, lacto-oligosaccharides	Support for microbiota, prebiotic effect
Enzymes	Trypsin, amylase, lipase, alkaline phosphatase	Digestion, metabolism
Soluble receptors	sCD14, cytokine receptors	Inflammation buffering, immune signaling
Acute-phase proteins	Lactoferrin, haptoglobin, α1-antitrypsin	Inflammatory response, tissue protection

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a serious, life threatening gastroenterological disorder affecting primarily premature or critically ill neonates and is characterized by acute inflammation followed by necrosis of the intestinal wall (Samuels et al. 2017). NEC is associated with a high morbidity, with overall mortality estimated at 25%, rising to up to 35% among neonates requiring surgical intervention (Jones et al. 2020). Many infants who survive NEC face long-term complications, such as neurodevelopmental impairments or intestinal failure (Adams-Chapman et al. 2018, Bazacliu et al. 2019).

NEC predominantly affects preterm neonates (born before 37 week of gestation or with birth weight under 1500g), due to immaturity of both immune and gastrointestinal systems. The most well-defined risk factors can be grouped into two categories: dysregulated, immature gut microbiota and reduced intestinal perfusion (Kaplina et al. 2023). A higher incidence of NEC has been documented in infants receiving diets composed exclusively of infant formula (IF), which lacks the bioactive, immunomodulatory compounds that are found in human breastmilk (Altobelli et al. 2020). Impaired tissue perfusion, often resulting from abnormal umbilical artery flow or conditions such as preeclampsia, also constitute a significant risk factor for NEC (Duci et al. 2019)

The pathogenesis of NEC is complex. One proposed mechanism involves overactivation of the Toll-like 4 receptor (TLR4) pathway in the immature intestinal epithelium of preterm neonates (Hackam et al. 2018). TLR4 activation by liposaccharides from Gram-negative bacteria induces enterocyte apoptosis and increases intestinal permeability, facilitating bacterial translocation and triggering a cytokine-mediated inflammatory cascade (Hunter et al. 2014).

Management of NEC is dependent on the severity of the condition. In milder cases, conservative treatment, such as antibiotics, full parenteral nutrition and gastric aspiration, is implemented. In more severe cases, especially those involving intestinal perforation, surgical resection of necrotic bowel segments is required (Stey et al. 2015).

NEC prevention focuses largely on reducing maternal and neonatal risk factors. Early diagnosis, structured screening programs and comprehensive risk management are crucial in reducing the burden of NEC. Beyond risk management, a few preventative interventions have been proposed. One of the most effective is early introduction of human milk, preferably mothers own milk (MOM) (Colarelli et al. 2024), which is widely supported in nutrition of preterm as well as term infants (Victora et al. 2016). Where MOM is not available or insufficient, human donor milk (HDM) is shown to have more benefits rather than IF (Quigley et al. 2019). Another preventative strategy includes cautious use of antibiotics. Most preterm neonates that are admitted to

NICU are administered antibiotics empirically which changes their intestinal microbiome and makes them more susceptible to NEC (Zwittink et al. 2018). Probiotics have also proven to be useful in regulating the immature microbiome and minimizing instances of NEC (Barbian et al. 2023).

Methodology

In this review paper, scientific literature is analysed to evaluate the effect of BC on prevention and management of NEC. An online database search was conducted using PubMed and Scopus, with keywords such as "Bovine Colostrum" and "Necrotizing Enterocolitis", along with their corresponding MeSH keywords. Only articles published from 2008 onwards were included in the review. Relevant animal studies and human randomized controlled trials evaluating the impact of BC on NEC incidence and severity were analysed.

Results and Discussion

Animal Models

Bovine colostrum (BC) has been promising in treatment and prevention of necrotizing enterocolitis (NEC), primarily due to well-documented therapeutic effects observed in animal models. However, the research findings are not entirely consistent. The results of the most relevant preclinical studies conducted on animal models are discussed below.

Comparison of Bovine Colostrum and Infant Formula

Various experiments have investigated whether BC is more effective in preventing NEC compared to infant formula (IF). In the experiment by Møller et al. (2011) preterm piglets delivered via caesarean section were given total parenteral nutrition for the first 6 hours after delivery and were then switched to enteral feeding for 48 hours. The research group was fed BC and the control was fed IF that was developed to mimic porcine milk. The BC group showed less frequent and much milder signs of NEC than the control group ($p<0.0001$). Møller et al. (2018) research should be interpreted with caution because both the control and the BC group were small in size.

In the study conducted by Støy et al. (2016) incidence and severity of NEC in preterm piglets fed BC, freeze-dried BC and pasteurized spray-dried BC were examined in comparison with a control group fed only porcine IF. In all three groups that received colostrum products enterally the NEC incidence and severity was lower than in formula-fed group. This experiment was also valuable because it assessed the outcomes depending on the method of colostrum processing. The NEC incidence and severity was the lowest in pasteurized spray-dried BC group, higher in spray-dried colostrum group and highest in the group fed fresh colostrum. The sample sizes were greater than in Møller et al. (2018) experiment.

Similar conclusions were obtained in Shen et al. (2015) experiment where one group of preterm piglets was fed with porcine IF and the other one with BC. There was higher incidence of NEC in the formula-fed group.

Comparison of Bovine Colostrum, Human Donor Milk and Infant Formula

The results of Møller et al. (2018) as well as Støy et al. (2016) appear to be consistent with the findings of Jensen et al. (2013) whose team investigated the incidence of necrotizing enterocolitis (NEC) in preterm piglets fed human donor milk (HDM), bovine colostrum (BC) and infant formula (IF) as a control. Both the HDM- and the BC- fed group showed a lower incidence of NEC (54%) compared to the formula-fed group (93%). However, no statistically significant difference in NEC incidence was observed between HDM and BC groups.

Research conducted by Rasmussen et al. (2016) supports the hypothesis that BC feeding in preterm piglets is superior to IF in preventing NEC. However, the findings are not fully aligned with results of Jensen et al. (2013) stating that BC and HDM have similar efficacy in prevention of NEC. In Rasmussen et al. (2016) study, BC-fed piglets had lower incidence of NEC than those in HDM group.

Comparison of Bovine Colostrum and Human Donor Milk

There are also documented experiments recording NEC incidence in piglets fed HDM fortified with BC. The experiment by Sun et al. (2018) investigated, among other outcomes, the incidence and severity of NEC in preterm piglets fed HDM and HDM fortified with BC (HDM+BC) and HDM fortified with a Nurtilon nenatal protein fortifier (HDM+FF). There were no significant differences in NEC incidence between the three groups, but the HDM+FF piglets exhibited more diarrhoea, higher bacterial density along intestinal villi and reduced intestinal enzyme activity compared to the HDM and HDM+BC groups. HDM+BC piglets had lower

colonic cytokine concentrations relative to the other groups. The findings of Sun et al. (2018) are partially supported by a study conducted by Sun et al. (2019), in which piglets fed DHM enhanced with fortifiers showed significantly higher diarrhoea scores, increased bacterial concentration and elevated gut permeability in comparison to the DHM+BC group. In the experiment led by Sun et al. (2019), however, there were significant differences in NEC incidence - HDM+BC pigs were characterized by fewer incidences of NEC in comparison to HDM+FF pigs.

Human Models

The outcomes concerning human preterm infants have proven less favourable for bovine colostrum (BC) supplementation compared to animal models.

In the double blinded, randomized, placebo-controlled study by Balachandran et al. (2016), preterm infants (n=86) were evenly assigned to BC and placebo groups. Infants in the BC group received supplementary BC mixed with MOM, in addition to the standard feeding regimen. The infants were closely monitored for development of necrotizing enterocolitis (NEC), sepsis and other adverse outcomes. There were no statistically significant differences in outcomes between the two groups, including NEC. Researchers found that there were more radiological signs suggestive of NEC in the BC group as well as more instances of intestinal wall oedema, pneumatosis intestinalis and pneumoperitoneum. However, after statistical analysis those findings were deemed not to be statistically significant. The mean interleukin-6 (IL-6) concentration, a pro-inflammatory cytokine associated with NEC, was also higher in the BC group (p=0.07). A limitation of the study was the use of an industrially processed, powdered BC product, containing BC microfiltrate and bovine immunoglobulin. Highly processed formula products have been linked to higher NEC incidence.

The findings by Balachandran et al. (2016) were partially replicated by Juhl et al. (2018). In a randomised, open-label, controlled trial, preterm infants (n=40) received supplementary BC feedings in addition to a standard protocol of MOM supplemented with IF when necessary. BC was formulated as a spray-dried, unmodified, intact colostrum powder, which was pasteurized and reconstituted before the administration. There were no significant differences in NEC incidence between the two groups, as no NEC cases were recorded in either group. No adverse side effects or feeding intolerances have been recorded in the BC group.

These outcomes were further reproduced in the recent PreColos study by Yan et al. (2023), involving a total of 350 preterm infants. Neonates randomly assigned to the BC group were given intact, unmodified, gamma radiated, pasteurised and spray-dried BC in an open-label trial, in addition to MOM. The control group received preterm infant formula as a supplement to MOM. No statistically significant difference in NEC incidence was found between the two groups.

Similar conclusions were drawn in the FortiColos study led by Ahnfeldt et al. (2023). In this Danish randomised, open-label, controlled trial, the effect of BC fortification of MOM or HDM were compared to conventional, bovine milk fortifiers. No clinical morbidities and adverse effects, including NEC, have been recorded in 232 preterm infants. As in the abovementioned studies, no statistically significant difference in NEC outcomes was observed between the two groups.

Conclusions

Even though bovine colostrum seemed promising in animal models, the human infant trials showed no effect of bovine colostrum administration on necrotizing enterocolitis incidence. The secondary outcomes such as weight gain, hospital stay duration, diarrhoea instances, intestinal bacterial concentrations and many others were inconsistent between the trials both in animal and human models. Lack of consistent outcomes makes it challenging to apply the findings of both animal and human trials more broadly.

One of the factors limiting the translation of the preclinical findings into practice seems to be the formulation and method of bovine colostrum administration in human trials. Experimental data from animal studies has shown that highly processed nutritional formulas can contribute to increased necrotizing enterocolitis risk, potentially by disrupting the gut homeostasis or altering the neonatal immune response (Call et al. 2018). In this context, the study by Balachandran et al. (2016) is worth investigating: the authors used a highly processed microfiltrate form of bovine colostrum and documented a higher incidence of adverse outcomes compared to other trials mentioned above. Moreover, the studies utilizing less processed bovine colostrum products such as spray-dried, irradiated, or pasteurized formulations have reported better safety profiles, although these products have not consistently demonstrated efficacy in minimizing necrotizing enterocolitis incidence. Future efforts in manufacturing bovine colostrum in human trials should focus on keeping its natural active ingredients while still making sure it is safe from harmful microbes.

Another limiting factor might be the open-label nature of the FortiColos, PreColos as well as Juhl et al. (2018) experiment. The results might have been influenced by the expectations of the parents and clinicians. A relatively high dose of scepticism towards bovine colostrum and preference for mother's own milk and human donor milk has been documented amongst parents resulting in high study-enrolment refusal rates (Dam et al. 2017).

While animal models continue to support the immunomodulatory and gut-protective potential of bovine colostrum, human trials have not demonstrated these benefits in necrotizing enterocolitis prevention. Well-designed, double-blind, placebo-controlled trials using standardized bovine colostrum products are needed to further assess the role of bovine colostrum in neonatal care.

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