Innovating Practice through Research and Evidence
Colostrum

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Introduction

Human colostrum is a vital first food tailored to assist the newborn’s transition to extrauterine life. During gestation, humans receive nutrients, immunological agents and growth factors from both the placenta and amniotic fluid. After birth, newborns must orally ingest what they need to survive. From colostrum’s typically small volumes to its unique composition, colostrum nurtures and protects human infants until they are ready and able to consume larger volumes of mothers’ milk.

Unlike humans, many mammals – for example, horses, pigs, cows and goats -- do not receive maternal antibodies in utero and for them, early ingestion of colostrum is absolutely essential for newborn survival; these animals attain gut closure within a day or so after birth, leaving very little time for intracellular absorption in the intestine of maternal colostral antibodies. If they do not receive colostrum before gut closure, they will die of infection from environmental pathogens.

Unlike these mammals, humans receive IgG antibodies via the placenta during the third trimester, which provide systemic immunity against specific diseases for approximately six months. After birth, newborns will receive additional but different immune globulins from mothers’ colostrum and milk to prevent mucous membrane invasion of the gastrointestinal and respiratory tracts. Secretory IgA is the most abundant immunoglobulin in colostrum. These mucosal-related antibodies bind to invading microbes, preventing them from attaching to and invading the mucosa. They are also capable of neutralizing bacteria, viruses and bacterial toxins and reducing the risk of inflammation.

In addition, colostrum provides infants with other antimicrobial components, as well as immunomodulatory and anti-inflammatory agents, growth factors, antioxidants and substances that promote tolerance and/or priming of the immune system. For preterm infants, colostrum is critically important as these infants miss some of the passive immunity conferred by placental IgG. Human colostrum contains high concentrations of many substances also found in mature milk: growth factors, antioxidants and anti-infective agents -- slgA, lysozyme, lactoferrin, macrophages, lymphocytes, and neutrophils.

This edition of Innovating Practice will explore three articles representative of important themes in the science of colostrum. The first article by Davanzo and associates describes the presence and concentration of an anti-tumor cytokine found in many human tissues, including human colostrum and milk. Commentary following a brief article summary will touch on a few of the many substances found in human colostrum, laying the groundwork for use of colostrum in neonatal intensive care.

The second article by Rodriguez and associates will explore colostrum administration as a form of immune therapy for preterm infants. This 2010 publication is one of the first clinical studies on the safety and feasibility of early colostrum administration in the NICU.

Lastly, a very recent publication by Miner and associates suggests colostrum has a unique role in the reduction of NEC progression from medical to surgical NEC. While many studies have identified human milk as a significant factor in the reduction of the incidence of NEC, this is the first publication isolating the benefits of colostrum in the progression this disease.

The overall theme in this edition related to colostrum is: the few days of colostrum production are a brief, but fascinating, period of time in which mothers produce their most densely concentrated milk. Through an understanding of research and clinical evidence, health professionals can ensure that infants receive the full benefits that colostrum confers.
Key Points

After birth, human newborns receive secretory IgA antibodies from mothers’ colostrum to prevent mucous membrane invasion of the gastrointestinal and respiratory tracts.\textsuperscript{1,4,5} These mucosal-related antibodies neutralize bacteria, viruses and bacterial toxins and reduce the risk of inflammation.\textsuperscript{6}

Colostrum also provides term and preterm infants with other antimicrobial components, as well as immunomodulatory and anti-inflammatory agents, growth factors, antioxidants and substances that promote tolerance and/or priming of the immune system.\textsuperscript{1,4,7-14}

For preterm infants, colostrum is critically important as these infants are born immunocompromised. Human colostrum contains high concentrations of human milk components including growth factors,\textsuperscript{15,16} antioxidants\textsuperscript{14,17,18} and anti-infective agents -- slgA, lysozyme, lactoferrin, macrophages, lymphocytes, and neutrophils.\textsuperscript{6,19}

A superfamily of cytokines called tumor necrosis factors can induce death in tumor cells. TRAIL -- or tumor necrosis factor–related apoptosis inducing ligand -- has just been identified in colostrum at levels 400 times higher than in human serum.\textsuperscript{20} Given its potential to kill malignant cells, TRAIL is currently under study as an anti-cancer therapy.\textsuperscript{21}

Unlike enteral tube feedings, oral administration of colostrum specifically exposes oropharyngeal-associated lymphoid tissues to many protective properties in colostrum.

Oral care and administration of colostrum present rich opportunities to engage and involve families in the care of their NICU infants. Sharing knowledge of the potential benefits of oral colostrum can help families, especially reluctant parents, commit to requests from NICU staff for expressed milk.

Human milk feedings have been associated with reduction in the risk of necrotizing enterocolitis (NEC) in a dose response manner. New research suggests colostrum feedings in the NICU might reduce the risk of necrotizing enterocolitis (NEC) progression from Bell’s stage II to Bell’s stage III, or from medical to surgical NEC.\textsuperscript{49}

Background

Laboratory researchers have identified a phenomenal number of components in human milk and colostrum. In previous Innovating Practice editions we have discussed many of these including commensal bacteria, human milk oligosaccharides (HMO), fatty acids and cholesterol. Of relatively new interest are the cytokines.

Cytokines are cell-signaling protein molecules secreted by many cells for the purpose of intercellular communication. In the context of human milk, cytokines are most recognized as having an immunomodulatory role in cellular communication during microbial invasion and infection. Cytokines can have opposing actions; they can trigger manifestations of disease like inflammation and cell death or they can act to suppress inflammation and promote cellular proliferation. Cytokines are also implicated in facilitating the differentiation of IgA-producing cells and the development of infant gastrointestinal and respiratory systems.

A review of current topics in human milk research reveals a recent increase in interest in milk cytokines. At least 27 cytokines, both pro- and anti-inflammatory, have been identified in colostrum and human milk. Pro-inflammatory cytokines such as interleukin 1 β (IL-1 β), IL-6 and IL-8 are present in variable amounts. However, human colostrum and milk contain anti-inflammatory cytokines in much higher concentrations. Amounts of these anti-inflammatory cytokines -- IL-10 and transforming growth factors β1 and β2 (TGF β1, TGF β2) -- would tend to down regulate potential inflammatory effects. In addition to inhibiting inflammatory responses, this second group of cytokines may promote cellular and tissue healing.

Cytokines are also involved in the ongoing process of cell death and regeneration. In healthy tissues, new cells are constantly being generated while older or damaged cells are dying. Apoptosis or programmed cell death is a mechanism to protect against excessive cellular growth, tumor growth and cancer.

A superfamily of cytokines called tumor necrosis factors (TNF) can induce death in tumor cells, controlling the growth of organs and tissues. TRAIL -- or tumor necrosis factor–related apoptosis inducing ligand -- is a tumor necrosis factor cytokine found in many human tissues, including breast tissues.

The purpose of this study was to determine the levels of soluble TRAIL in human colostrum, breastmilk, serum and infant formulas. To meet this end, the authors obtained 55 colostrum and 17 breastmilk samples from healthy mothers of term infants. They obtained 40 human serum samples from a blood bank. To investigate the presence of TRAIL in infant formulas, they sampled seven types of ready to feed formula.
Results

The authors found:

- The median TRAIL value in colostrum was 19.87 nanograms/mL
- The median TRAIL value in breastmilk was 9.57 nanograms/mL
- The median TRAIL value in human serum was 67 picograms/mL
- TRAIL was not detected in any of the infant formulas

Conclusions

TRAIL is present in human colostrum, milk and serum in strikingly different concentrations.

TRAIL levels are 400 times higher in colostrum than in human serum. TRAIL concentrations in human milk decline in the first 4-5 days after delivery but are still higher in milk than in serum.

The levels of TRAIL in human colostrum and milk are within the range of concentrations that can kill cancer cells.

The authors concluded the presence of TRAIL in colostrum and milk may be associated with the reduced risk of certain cancers in children who were breastfed, specifically, lymphoblastic leukemia, Hodgkin’s disease and neuroblastoma.

Commentary

This study is an excellent example of the discovery of a potentially beneficial substance, occurring in high concentrations in colostrum, and, to a lesser extent, in mature human milk. Although the relationship of TRAIL to infant or maternal outcomes is theoretical at this time, the presence of such high levels of TRAIL suggests there are reasons for its presence.

In earlier studies, researchers determined that TRAIL, unlike other tumor necrosis factors, could induce apoptosis of tumor cells in vitro and in vivo with minimal or no toxicity on normal cells and tissues. In a review of studies on TRAIL, Di Pietro and Zauli22 reported effective but selective killing of tumor cells from lung, breast, kidney, colon, prostate, thyroid and skin cancers by TRAIL without harmful effects to healthy cells. Given its potential to kill malignant cells, TRAIL is currently under study as an anti-cancer therapy.21 In the above study, Davanzo and associates hypothesized TRAIL may have a role in the ability of human milk feedings to decrease certain cancers in children.

Given the exceptional levels of TRAIL in colostrum identified by Davanzo et al, we will look forward to future research on properties and clinical applications of TRAIL. Until that time, it is worth reflecting on the purpose of high concentrations of cytokines in colostrum. In 1991, Bocci and associates24 asked “What is the role of cytokines in human colostrum?” They proposed the first, if not primary, site of action for colostral cytokines is the oropharyngeal-associated lymphoid tissue (OFALT) in infants’ tonsils and adenoids. They explained these tissues "behave like a sponge" taking in cytokines which then activate local immune cells as well as those in distant organs. Despite small colostral volumes produced in the first few days, the amount is sufficient to coat OFALT systems in newborn infants. Bocci et al24-26 have studied therapeutic oropharyngeal administration of interferons from human milk, proposing the oral mucosa is often overlooked as a potential site of action for administration of therapeutic substances. In the next section we will explore a study of oropharyngeal colostrum administration to preterm infants in the NICU.
Background
Preterm infants, especially extremely low birth weight (ELBW) infants, are at high risk for nosocomial infection.

Own mothers’ milk (compared to formula) has been shown to decrease the risk of infections in ELBW infants; however, many ELBW infants are not able to take enteral feeds immediately after birth.

Oropharyngeal administration of colostrum is a potential alternative method for giving own mothers’ colostrum.

Human colostrum contains multiple immunoprotective substances including cytokines, lactoferrin and human milk oligosaccharides (HMOs). Cytokines in colostrum may stimulate lymphatic tissue responses to protect against infection while HMOs – like IgA antibodies -- are believed to prevent adhesion of bacteria to mucosal surfaces. Unlike enteral tube feedings, oral administration of colostrum specifically exposes oropharyngeal-associated lymphoid tissues (OFALT) to these protective properties, activating the acquired immune system. Furthermore, IL-6 – a cytokine in mothers’ milk – stimulates infant’s lymphocytes to become IgA-secreting plasma cells.27-32

In addition, very small amounts of orally administered colostrum are swallowed with saliva. When they reach the intestine, colostral cytokines may stimulate sIgA production in gut-associated lymphoid tissue (GALT), activating a separate locus of acquired immunity. Therefore, colostrum might provide protection from mucosal pathogens, potentially reducing the risk ventilator-associated pneumonia (VAP) in ELBW infants.30,31

Studies in adults have indicated that small amounts of liquid placed on the oral mucosa can be absorbed by the mucous membranes and OFALT system. Indeed, the oropharyngeal administration of an immune cell-derived cytokine, interferon-α, seems to be safe and may have stimulating effects on immune response.24-26,30,31

Therefore, the purpose of the study was to evaluate the safety and feasibility of oropharyngeal colostrum administration in the first few days of a preterm infant’s life. A second purpose was to determine the feasibility of measuring both S IgA in tracheal aspirates and lactoferrin in urine as indicators of colostrum absorption and effectiveness.

Five mothers and their ELBW infants participated in this pilot study. Infants’ mean birth weight was 657 grams and mean gestational age of 25.5 weeks.

 Mothers expressed colostrum as soon as possible after delivery. Beginning within 48 hours of life, 0.1 mL of colostrum was administered very slowly by needleless tuberculin syringe to each side of the posterior buccal mucosa (a total of 0.2 mL or approximately 14 drops per treatment). Treatments were done every two hours for 48 hours. Infant vital signs and oxygen saturation were continuously monitored.
Results
All infants tolerated every treatment procedure without adverse changes in vital signs or oxygen saturation. For all infants, oxygen saturation levels either remained stable or increased during colostrum administration. All infants began to suck on the endotracheal tube during administration of colostrum.

Data from tracheal aspirates and lactoferrin levels in urine samples varied widely making data difficult to evaluate. Also, inadequate samples in some cases and lack of reference values in ELBW infants prevented analysis of laboratory measures.

Conclusions
The authors found that oral administration of colostrum to ELBW infants was feasible and well tolerated. All mothers were able to produce enough colostrum (4.8 mL) needed for two days of treatment.

They concluded future studies are needed regarding infection outcome measures and reference values for immune system markers.

Commentary
This clinical study is the first to propose therapeutic oral administration or oral care with mothers’ own colostrum for preterm infants. Although outcome measures were physiologically inconclusive, it must be noted that this study was a pilot study to determine the safety of the procedure. Indeed, it is of interest that extensive research supporting the use of human milk as medicine and the authors’ logic for colostral oral administration seems to have made a significant impact on NICU practice policies and procedures in the United States. As such, many authors and hospitals, citing this research, now recommend colostrum administration and oral care for preterm infants: Arnold’s Human Milk in the NICU: Policy to Practice;33 Meier and associates;34 Spatz and Edwards;35 and Spatz.36 Furthermore, carrying this work forward, Pinkerton and Wilkinson37 are progressing this research with regard to buccal care with colostrum in low birth weight infants.

It is of particular importance that Rodriguez et al30,31 mention the possibility of colostrum administration reducing ventilator associated-pneumonia (VAP) in NICU infants. However, at this time there is interest but no specific studies related to this outcome. Given the national prevalence and seriousness of VAP in preterm infants, this is an area worthy of further investigation.

Until that time, oral care or administration of colostrum presents rich opportunities to engage and involve families in the care of their NICU infants. Rodriguez et al31 briefly mentioned mothers’ willingness to participate in this study because they wanted their infants to have the opportunity to taste their colostrum weeks or months sooner than they normally would. Involving families in delivery of colostrum to the NICU and allowing them to participate in colostrum administration sends a powerful message regarding the value of every drop of mother’s milk.34-36 In addition, knowledge of potential benefits of colostrum may influence breast-pumping decisions in the critical, early days after delivery.

The next section will explore a 2013 study of mothers’ own colostrum as a possible factor associated with reducing the severity of necrotizing enterocolitis.

Background

Necrotizing enterocolitis (NEC), occurring at a rate of 1-5 per 1000 live births, is estimated to affect approximately 10% of preterm infants less than 1500 grams. Infants with NEC require NICU care, with the most severe cases requiring surgical treatment. Mortality rates for NEC in general are greater than 20%, rising to 30-40% if surgical treatment is required.

Bell’s system, later modified by Walsh, identifies three stages of NEC in progressing order of severity. Stage I disease presents as feeding intolerance, abdominal distention and bloody or heme-positive stools. Stage II includes these symptoms plus radiographic findings of pneumatosis intestinalis. Stage III NEC includes stage II criteria with the addition of need for surgical intervention. Factors associated with the increasing disease severity are poorly understood.

Preventing surgical NEC could reduce infant mortality and reduce costs of care for preterm infants.

The purpose of this study was to identify factors associated with NEC severity, specifically progression of NEC from medical to surgical management. Data were obtained from retrospective chart reviews -- including radiographic images, surgical and pathology reports -- of 220 infants with diagnoses of confirmed NEC, Bell’s stages II or III. Four patients had more than one episode of NEC, therefore, 225 episodes of NEC were evaluated: 157 episodes of Bell’s stage II and 68 episodes of Bell’s stage III.

Multiple maternal and neonatal characteristics were included in statistical analyses as well as treatments, laboratory data and infant feeding types prior to NEC diagnosis.

Feeding types included mother’s own milk including early colostrum feedings in days 1-5, pasteurized donor human milk, formula and fortified mother’s own milk.

Stepwise regression was performed to identify variables that were significant predictors for NEC progression.
Results

Earlier gestational ages and lower birth weights were associated with a greater risk of stage III NEC. Additionally, infants born at younger gestational ages tended to develop NEC (stage II and III) at later post-conceptual ages.

Abnormal laboratory values (C-reactive protein, I/T neutrophil ratio, blood pH, leukocyte count, mean platelet volume, platelet count) within three days prior to NEC diagnosis were more common in infants who developed stage III disease.

Variables predicting a reduced risk of stage III NEC were:
1) Earlier feedings (within the first five days) of mothers’ own milk (Colostrum) (OR 0.80; CI 0.67-0.96)
2) Diagnosis at an earlier post-conceptual age NEC (OR 0.94; CI 0.91-0.97)

Variables best predicting death from NEC were:
1) Lower blood pH prior to NEC diagnosis (OR 2.21; CI 1.27-3.85)
2) Lower percentage of colostrum and early feedings with mother’s own milk. (OR, CI not given)

The authors noted that for every 1% increase in early mothers’ milk feedings (colostrum), there was a 4% reduction in the probability of death from NEC.

Conclusions

Several variables such as earlier gestational age, lower birth weight, later post-conceptual age at diagnosis and abnormal labs at the time of NEC diagnosis may indicate a higher risk of disease progression. Of the factors in this study associated with NEC progression to stage III, only infant feedings and blood transfusions are potentially modifiable variables.

Study results suggested early administration of mothers’ own colostrum seemed to have a protective effect, in a dose-response manner, against the risk of surgical NEC and death.

Reducing the severity of NEC can lower disease-related costs and improve infant outcomes. Further investigations of blood transfusions and early colostrum feedings are needed to clarify their effects on disease progression in NEC.

Commentary

Many studies have associated human milk feedings with decreased risks of NEC or death in preterm infants. Classic studies by Lucas and Cole, Schanler and associates, Meinzen-Derr et al, and Sisk et al demonstrated human milk feedings in the NICU contributed in a dose response manner to reductions in NEC and mortality associated with NEC. In a similar vein, Taylor et al found higher percentages of human milk feedings in the first 28 days of life reduced gut permeability when compared to formula feedings. In these studies, colostrum volumes were included in human milk amounts or percentages of feeding volumes. The above study by Miner and associates is the first to isolate colostrum feedings, defined as early feedings with the first 5 days of life, as protective against progression of NEC from Bells’ stage II (medical NEC) to stage III (surgical NEC).
In discussing their results, Miner and associates distinguished between early feedings of mothers’ own colostrum and pasteurized human donor milk. Processes for storage of human milk were not discussed. Since this retrospective study included NEC cases from multiple sites over a span of eight years, it is likely some colostrum feedings were fresh samples, which are known to have the greater bioactivity than milk that has been frozen or heat-treated. Donor human milk is generally comprised of pooled mature milk from multiple donors; thus, even prior to heat treatment it is not as concentrated as fresh colostrum in many of the immunologic, anti-inflammatory and protective substances.

Criteria for the use of donor milk were not specified and although donor milk was used, it was not observed to have the same protective effect as mothers’ own early milk (colostrum). The authors identified several differences in donor human milk compared to mothers’ own milk that may have been associated with study results. These include destruction of leukocytes and reduction of slgA and IgG, lactoferrin, lysozyme, some anti-inflammatory cytokines and selected growth factors as consequences of pasteurization. Some of these reductions occur with human milk freezing, a part of the process of preparation of donor milk for distribution.

As a retrospective data analysis, this study by Miner et al proposes a testable theoretical relationship between early colostrum feedings and reduction in NEC severity. The results suggest early and consistent colostrum feedings possibly abate the progress of a potentially devastating disease in preterm infants. These results do not negate findings of previous studies related to use of human milk and reduction of the incidence of NEC but rather highlight the importance of colostrum in the very early, critical period after birth.

Concluding Remarks

Human colostrum, highly concentrated early milk, assists infant transition from intrauterine to extrauterine life. Although volumes of colostrum are small, high concentrations of antimicrobial agents, antibodies, cytokines and anti-tumor factors (along with many other components) inspire a growing appreciation of the role of colostrum in healthy human growth and development.

In this document we have touched on research related to potential benefits of colostrum. Additional clinical studies are needed to verify the potential benefits of colostrum as suggested by the authors highlighted in this essay. Many clinical practices in this area are in the early stages of research and development, however, the science suggests the practices discussed in these studies: 1) do no harm, and 2) are potentially beneficial, especially to preterm infants. Colostrum production after birth lasts just a few days; consequently, clinical studies of its effects are challenged by short exposure periods and commingling of colostral effects with those of transitional and mature milks.

Without a doubt, progression of lactation science from laboratory settings to descriptive studies to clinical trials will uncover and substantiate further advantages of early human milk administration and feeding. These research findings, consequently, will need to coalesce with evidence-based policies, procedures and techniques to promote the best possible outcomes for mothers and their infants.
References

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