Bovine Colostrums: A Review of Clinical Uses

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Abstract

Bovine colostrums are the "early" milk produced by cows during the first several days post-parturition. This "early" milk has a nutrient profile and immunological composition that differs substantially from "mature" milk. Included in the nutrient profile are higher amounts of immunoglobulins, growth factors, cytokines, and nucleosides than are found in milk. Bovine colostrums are also rich in oligosaccharides, antimicrobials, and immune-regulating factors. Available evidence suggests a beneficial effect of supplementation of bovine colostrums in improving body composition, aspects of athletic performance, diarrhea in persons with immune-deficiency syndromes, NSAID-induced gastrointestinal disturbances, and aspects of the acute phase response that occurs secondary to surgery. Specific hyperimmune bovine colostrums, produced to have high neutralizing titer activity against Cryptosporidia, *H. pylori*, measles, rotavirus, and *Shigella sp*., appear to have clinical utility in conditions associated with these infectious organisms.

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Introduction

Bovine colostrums (BC) are the "early" milk produced by cows during the first several days post-parturition. This "early" milk has a nutrient profile and immunological composition substantially different from "mature" milk. In addition to macronutrients found in milk such as protein, carbohydrate, and fat, and micronutrients including vitamins and minerals, BC contain oligosaccharides, growth factors, antimicrobial compounds, and immune-regulating constituents either not present in milk or present in substantially lower concentrations.[1] The comprehensive nutritional, growth factor, and immune support is thought to provide passive immunity to protect the newborn calf from opportunistic infections while the immune system is developing, as well as to facilitate the growth and immune maturation of the digestive tract and possibly other tissues.[1]

The use of BC as a dietary supplement has increased substantially over the past decade. Unlike some dietary supplements whose composition is precisely defined chemically, and hence could be expected to be similar in composition irrespective of the brand, BC do not have a typical composition profile. Multiple factors influence the composition of BC, including the breed and health status of the cow, feeding practices, and time collected post-parturition. For example, a product made from BC collected during the first 24 hours post-parturition would be expected to have a higher concentration of immunoglobulins (Ig) and growth factors than a product made from BC collected from the same cows during the first three days post-parturition. In much of the existing research, specifics about collection time were not described within the methodology; in other cases, collection times were precisely defined. When reviewing the literature, if specific collection criteria were utilized, it is stated when the study is described.

While all BC contain neutralizing Ig against enteric pathogens, the specific Ig and the neutralizing titer of Ig contained is less predictable

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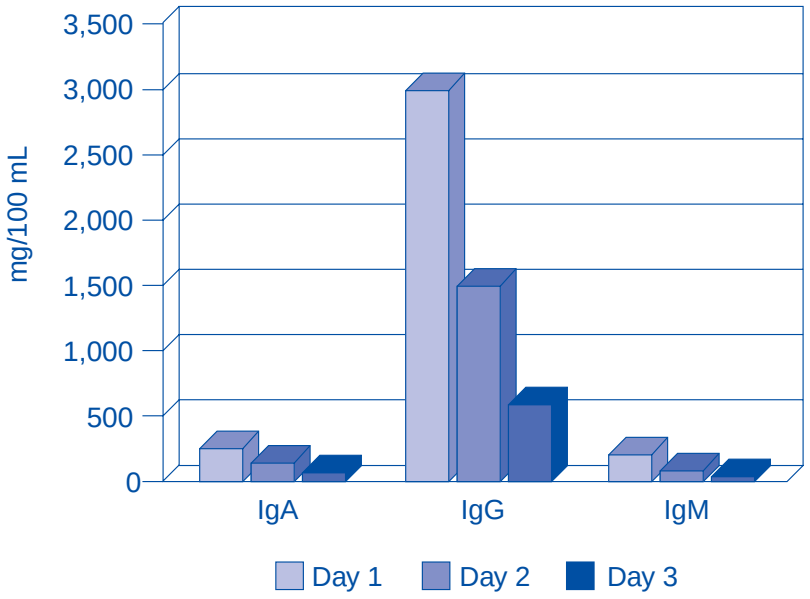
Figure 1. *Decline of Immunoglobulins in Bovine Colostrums (mean of 12 colostrums collected) during the First Three Days Post-parturition*



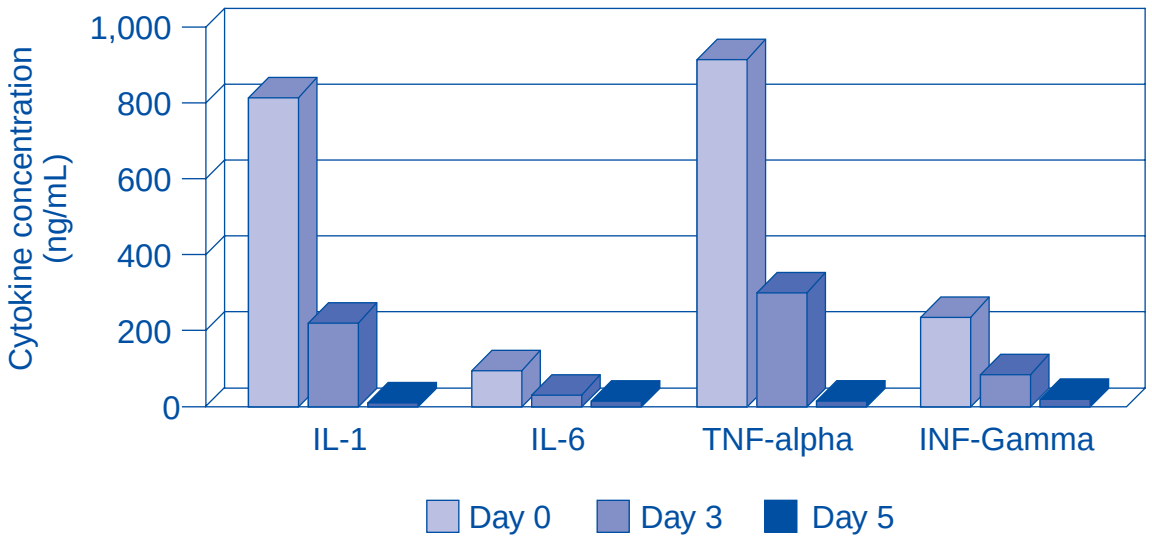
and is dictated by previous immune system challenges. For example, in cows exposed to a specific immunological challenge such as rotavirus, the BC produced might contain a relatively high neutralizing Ig titer against this virus (as well as many other pathogenic microorganisms). Conversely, BC collected from cows never exposed to rotavirus, while containing similar amounts of Ig against a variety of pathogens, might have no specific neutralizing Ig against rotavirus. This is an important distinction, since a large percentage of the research on BC, as prophylaxis or treatment for infectious disease, has been focused on products that are, as a consequence of specific immune provocation, immunologically unique. For the purposes of this review, BC produced by immunizing cows against specific microorganisms will be referred to as "hyperimmune bovine colostrums" (HBC). The clinical results produced by specific HBC cannot necessarily be generalized to other HBC utilizing different immunizations nor to BC from non-immunized cows. When discussing research on HBC, the manner the immune system was challenged will be briefly reviewed. Readers wishing more information on methods used to generate a specific HBC product can find additional details on methodology in the original research.

Post-collection processing and concentration methods used by suppliers of BC also influence the quantity of specific constituents in bovine colostrums, and hence, possibly clinical effects. For example, two BC products initially could have similar constituent profiles when collected; however, after processing and concentrating, these two products could have very different quantities of protein (Ig, lactalbumin, casein), fat, lactose, and lactoferrin.

Because of the factors influencing the composition and quantity of constituents within BC, rather than thinking of BC as a specific substance, it is both more accurate and appropriate, especially when reviewing the existing literature, to think of BC as a category – within which often exist more precisely defined products. Therefore, the immunological and clinical impact produced by specific BC or HBC products discussed in this review cannot necessarily be presumed to be a result that will be produced by all BC.

This review focuses exclusively on the potential uses of BC as dietary supplements. Although BC have been used as enemas in the treatment of distal colitis,[2] as a component of oral hygiene products in persons with primary Sjogren's syndrome and oral lichen planus,[3] as a component of a mouth rinse to determine the effect on dental plaque,[4] and as a component of a tear substitute in persons with dry eyes,[5] since dietary supplements are defined as being taken orally and results generated by other methods of

Figure 2. *Declines in Cytokine Concentrations in Bovine Colostrums Post-parturition (concentrations in ng/mL)*



administration cannot necessarily be generalized to oral dosing, the several studies utilizing BC delivered other than by oral dosing are not discussed in this review.

Overview of the Production of Bovine Colostrums and Hyperimmune Bovine Colostrums

While BC are considered a rich source of Ig, growth factors, and lactoferrin, currently no specific standards exist that define BC dietary supplements with respect to actual constituents or amounts of constituents. The following constituents are generally present in bovine colostrums: macronutrients; vitamins; minerals; Ig (IgG, IgM, and IgA – including the secretory form); cytokines including interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (INF-γ); growth factors including insulin-like growth factor (IGF) I and II, transforming growth factor-beta (TGF-β), and epidermal growth factor; lactoperoxidase; and lactoferrin. Depending on the health of the cows, feeding practices followed, collection period, and the processing/concentration practices utilized by specific manufacturers, the actual range and quantities of specific macro- and micronutrients, Ig, cytokines, growth factors, and other compounds might vary considerably.

As noted above, BC are defined as the milk collected during the first "several days" post-parturition. "Several days" has no definable standard attached; however, it is generally considered that milk collected more than four days after calving is no longer considered BC. Some products are exacting with respect to collection times and might only use milk collected during the first 12 hours post-parturition. Other products might use a collection time cut-off of 24 hours post-parturition, while others might use 3-4 days. The primary reason for concern over specificity of collection time is that BC produced during the first hours after calving have higher concentrations of specific bioactive constituents. Ig, growth factor, cytokine, oligosaccharide, and nucleotide content of BC reach maximum concentration the first 24-48 hours post-parturition. Concentrations of these constituents (and possibly others) decline substantially in a time-dependent manner following peak

concentration.[1,6-8] Figures 1 and 2 show the decline in specific Ig and cytokines that can occur the first several days after calving.

BC contain relatively high amounts of Ig. Typically, Ig in general, and IgG specifically, constitutes the largest contribution to protein content in BC, with lactalbumin and casein contributing lesser amounts. Table 1 provides a breakdown of Ig content for one product collected during the first 10 hours post-parturition.[7] Other reports have estimated Ig concentrations from bovine mammary secretions with ranges for IgG1 (52-87 g/L), IgG2 (1.6-2.1 g/L), IgM (3.7-6.1 g/L), and IgA (3.2-6.2 g/L).[9] As a rule, the Ig contribution will decline substantially in any BC collected more than 24 hours post-parturition and the amount of lactalbumin and casein will increase proportionately.

Additional processing of BC is often undertaken to concentrate the Ig component. In order to generate a product high in Ig, processing typically includes pasteurization, powdering, and removal of most of the milk fat, casein, lactalbumin, and lactose (with subsequent concentration of the Ig-protein component). Depending on the intensity of processing and concentration used, as few as 2-5 kg of dry powder might be produced from 100 kg of initially collected BC.[10,11] Some studied products have concentrated the protein content to approximately 85 percent and have specifically listed an Ig content.[12] Other studied products, while undergoing processing to ensure a high protein content, have not determined the Ig content of the preparation.[13] Because different collection, manufacturing, and concentration processes used in various research can result in different Ig concentrations, 10 grams of BC used in one study might have a substantially different content of Ig than an apparently similar 10 g dose used in a different study.

Table 1. *Immunoglobulin Composition of Bovine Colostrum Collected During the First 10 Hours Post-parturition*

Constituent	Concentration (g/L)
IgG	30.4
IgA	3.5
IgM	9.6

Adapted from: Stephan W, Dichtelmüller H, Lissner R. Antibodies from colostrums in oral immunotherapy. *J Clin Chem Clin Biochem* 1990;28:19-23.

Although BC contain Ig to neutralize enteric pathogens, the titer of the Ig present is considered by some researchers too low to afford protection against specific infectious organisms.[14] This limitation is overcome by using one of three methods: collection of BC during a more narrow time period post-parturition; concentration of Ig; or production of HBC.

Several uncontrolled intervention trials have been conducted using only BC collected during the first 10 hours post-parturition.[7,15,16] The rationale behind this collection procedure as opposed to a several-day period post-parturition is to produce products with higher amounts of Ig against microbes and their toxins, and to create a means for improved standardization of the BC product. When referring to this collection practice, Stephan et al stated, "The immunoglobulin content is so high that immunization of the cow... is unnecessary."[7] As can be seen in Table 2, the BC collected in this manner have a relatively high neutralizing Ig titer against a range of pathogens.[7,15]

Advances in fractionation technologies have enabled the large-scale isolation of Ig from BC, which allows for concentrating higher amounts of Ig than would otherwise be found in bovine colostrums. Theoretically, higher concentrations of Ig might be expected to afford enhanced passive immunity.[17]

Production of HBC by immunization of cows against specific pathogens during pregnancy has also been proposed as a method to overcome the limitation of low Ig content, as well as the nonspecific nature of existing Ig in BC. As a result of

specific immunizations, cows produce HBC with increased amounts of specific Ig. For example, a HBC intended as a treatment for shigellosis was created by intramuscular vaccination of pregnant cows with a heat-killed *Shigellosis dysenteriae* type I organism. After priming the immune system with the vaccine, two subsequent intramammary infusions of the vaccine were given at two-week intervals. The resulting HBC produced and collected was far higher in specific neutralizing titers of *S. dysenteriae* type I antibody than BC from cows that did not receive the immunization protocol. The intent of intramammary introduction of the vaccine in this case was to produce an improved mucosal immune response.[18] While not all HBC utilize an intramammary challenge, some data suggest that prior exposure of mammary cells to a virus or bacteria might be a prerequisite for local production of antibody and presence of a virus or bacteria in the blood does not necessarily mean mammary cells will be exposed to the microbial antigens.[19]

While the specific methodology varies (including organism used, inoculation route, and frequency of administration), all HBC have specific inoculation protocols designed to increase antibody content as a common feature. Inoculation typically occurs during a cow's "dry" period and is repeated several times. Health status of the cow is also considered important in determining antibody response when producing hyperimmune products.[17]

Table 2. *Antibody Activity of Bovine Colostrums Collected During the First 10 Hours Post-parturition*

Antigen	Reciprocal Antibody Titers Contained
Escherichia coli	640
Escherichia coli J5	640
Pseudomonas aeruginosa	640
Klebsiella pneumoniae	640
Proteus vulgaris	80
Serratia marcescens HY	1280
Salmonella typhimurium	160
Staphylococcus aureus	640
Staphylococcus epidermidis	160
Staphylococcus pyogenes	160
Staphylococcus faecalis	160
Staphylococcus viridans	640
Streptococcus B	80
Candida albicans	320
Cryptosporidia oocysts	100
Campylobacter jejuni (outer surface antigens)	1280
Helicobacter pylori	640
Yersinia enterocolitica YOP1 (outer membrane proteins)	1280
Shiga-like toxin I	1600
Shiga-like toxin II	3200
E. coli heat unstable enterotoxin (LT)	100
Rotavirus	32

Adapted from: Stephan W, Dichtelmüller H, Lissner R. Antibodies from colostrums in oral immunotherapy. *J Clin Chem Clin Biochem* 1990;28:19-23. Rump JA, Arndt R, Arnold A, et al. Treatment of diarrhoea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrums. *Clin Investig* 1992;70:588-594.

Clinical Research on Bovine Colostrums

Body Composition and Exercise Performance

Several studies have examined the impact of supplementing the diet with BC on body composition and exercise performance. In studies to date, participants had been previously training, and in several trials participants were elite-level athletes. While existing studies are presented in more detail below, the findings of these studies suggest several generalizations. First, BC supplementation might increase IGF-I levels; however, due to the relatively brief intervention period and other aspects of the study discussed below, no firm conclusions can be drawn. In the only study that looked at hormones associated with body composition and/or exercise performance, supplementation with BC did not produce significant changes. Second, in the trials completed on the elite-level athletes, BC supplementation appeared to positively influence exercise performance characterized by short bursts of activity; however, it did not appear to influence endurance performance. Third, in elite-level athletes, supplementation has not been found to improve body composition. Conversely, in non-elite athletes who were actively weight training prior to supplementation, BC improved body composition but produced no statistical impact on aspects of strength performance.

BC are a rich source of growth factors including an IGF-I structurally identical to that found in humans.[20] Since IGF-I has an anabolic effect and is involved in the regulatory feedback of growth hormone, the effect of supplementing the diet with BC on serum and muscle levels of IGF-I was investigated in athletes.[21] Nine male track athletes (sprinters or jumpers) were recruited to participate. The study was designed as a randomized, double-blind, crossover trial. The active intervention consisted of two divided doses of either 25 mL BC mixed with 100 mL placebo (IGF-I concentration of 13.5 mcg/L) or 125 mL BC beverage (IGF-I concentration of 67.6 mcg/L). Placebo consisted of an equivalent amount of milk whey. Over the eight-day intervention period, serum IGF-I increased in a linear fashion in the participants receiving the 125 mL daily BC dose. Despite this, the actual average daily serum IGF-I increase was quite low (0.54 nmol/L) and did not reach levels outside the range found with normal day-to-day variability. While the increase did reach statistical significance when the change was assessed from baseline to end of the 125 mL daily intervention, the actual quantity of IGF-I in the serum after the eight-day trial was similar in all groups and no statistically significant differences were found among groups. The statistically significant increase in IGF-I in the 125 mL group could be explained by higher baseline IGF-I concentrations in the placebo and 25 mL groups. In fact, baseline values in the placebo group were higher than the ending values of IGF-I in any group. No significant differences in insulin, testosterone, growth hormone, or cortisol levels were observed among groups. No significant impact on secretory IgA or serum IgG was observed. Jumping performance was also examined and no measurable difference was observed among groups.

In order to assess the impact of supplementing the diet with BC on body composition, 22 men and women were recruited who had already been performing resistance exercise training at least three times weekly for six months. Participants supplemented their diets for eight weeks with a mean daily dose of either 20 g BC powder or a whey protein concentrate as placebo. The BC preparation was approximately 80-percent protein. The concentrations of other bioactive constituents, including lactoferrin, growth factors, and immunoglobulins, were not determined. Changes in the amount of weight lifted in a one-repetition maximum bench press and the maximum number of repetitions did not reach statistical significance when comparing BC to the whey placebo or when comparing pre- and post-supplementation periods for active or placebo interventions. Body composition analysis was conducted using dual-energy x-ray absorptiometry (DEXA). A statistically significant increase in lean body mass was observed in participants supplementing with BC, with an average increase of 1.4 kg. An average reduction in body fat mass of 0.72 kg was also observed in subjects consuming BC, but this decrease did not reach statistical significance; an insignificant increase in weight of 1.10 kg was

observed. Subjects supplementing with whey protein concentrate had a statistically significant increase in weight (2.11 kg), while average lean body mass decreased by 0.11 kg and average fat mass increased by 1.45 kg. This suggests the statistically significant increase in weight was not a result of increased lean body mass, but was a result of a combination of increased fat deposition and changes in hydration status.[13]

A double-blind, randomized, placebo-controlled study investigated the effect of eight weeks of supplementation with BC on body composition and exercise performance in 17 female and 18 male elite field hockey players. Subjects received either 60 g BC daily or a whey protein concentrate as a placebo. While improvements in sprint performance occurred in both active and placebo groups, a significantly greater improvement was observed in subjects receiving BC compared to placebo. No statistically significant improvement in vertical jump performance was observed as a result of BC supplementation. No significant changes in body composition or measures of endurance were observed between the two groups.[22]

A randomized, double-blind, placebo-controlled trial on the effects of bovine colostrums on performance and body composition was conducted on 13 elite female rowers. Six subjects received 60 g BC daily and seven subjects received a similar amount of whey protein concentrate as a placebo during nine weeks of pre-competition training. The distance covered and work performed during a four-minute maximal rowing effort was significantly greater in the group receiving BC.[23] These results suggest supplementation with BC improves certain aspects of rowing performance in elite female rowers.

Immunodeficiency-Related Diarrhea

A combination of case reports and clinical trials suggest BC and HBC might be of benefit for the treatment of chronic diarrhea among persons with immune deficiency syndromes. As a rule, supplementation resulted in improved stool volume and decreased frequency. Supplementation also resulted in complete resolution of previously non-responsive diarrhea in some immune-compromised individuals. Diarrhea caused by *Cryptosporidium parvum* is common among persons with immunodeficiency syndromes. Supplementation with specific HBC with high neutralizing titer against this organism or with BC collected within the first 10 hours post-parturition may be particularly effective if the chronic diarrhea is associated with Cryptosporidia.

Several isolated cases of the effective treatment of Cryptosporidia-related diarrhea in immune-compromised individuals using HBC (collected from cows immunized with Cryptosporidium antigens) have been reported in the literature. Individuals in the case reports had chronic diarrhea that had failed to respond to conventional treatment. Individuals also had stools positive for Cryptosporidia oocysts. Because of the clinical condition of some patients, the HBC preparations were delivered via nasogastric tubes in several cases. Subsequent to intervention with HBC, stool volume and frequency was normalized in many individuals and, in some cases, remained normalized during long-term follow-up. When positive results were obtained, resolution of diarrhea typically occurred within 3-10 days post-commencement of the intervention; in several cases, the intervention resulted in stool culture becoming negative for oocysts. In other cases, reduction in oocyst load was less dramatic than improvement in stool volume and frequency.[24-28]

Three uncontrolled trials administered BC products and monitored changes in stool frequency in immune-compromised persons. The BC utilized in these uncontrolled trials (results described below) were collected during the first 10 hours post-parturition, assayed, and found to have Ig with specific activity against the pathogens listed in Table 2.

Twenty-nine AIDS patients were treated for 10 days with 10 g per day of a BC product concentrated for Ig. The average daily stool frequency decreased from 7.4 to 2.2 by the end of the 10-day treatment period. Four patients were considered non-responders and did not benefit from the intervention. After discontinuation of the dietary supplement, 12 patients re-experienced diarrhea, while 14 remained free from diarrhea for at least four weeks. Cryptosporidia had been found

in the stools of four persons in the trial prior to the intervention. After the 10-day intervention, levels of this microbe were undetectable.[7]

Thirty-seven patients with chronic diarrhea (more than four stools daily for greater than two weeks) participated in an uncontrolled trial to assess the effect of daily doses of 10 g BC for a 10-day trial period. Patient distribution was as follows: 29 HIV-infected, two with common variable immunodeficiency (CVID), one with an unidentified immunodeficiency, and five with graft-versus-host disease (GVHD). Any person who suffered a relapse of diarrhea received BC for a second 10-day treatment period. Twenty-one persons infected with HIV, two with CVID, the one person with an unidentified immunodeficiency, and four with GVHD responded to BC with either transient or long-lasting normalization of stool frequency. In this group of responders, mean daily stool frequency decreased from 7.0 to 1.1. Prior to the intervention, *Giardia lamblia* was detected in stools of two persons, *Blastomyces hominis* in one stool, and *Campylobacter jejuni* in one stool. These organisms were not detected on follow-up stool analysis conducted post-intervention. Cryptosporidia were detected in the stools of seven persons prior to the intervention; five were free of this organism after the first 10-day BC period. One additional person became Cryptosporidia-free after a second 10-day period of BC supplementation. Of the people who responded to the intervention, approximately two-thirds remained diarrhea-free during a four-week follow-up period.[15]

Twenty-five HIV-positive patients (16 of whom met the complete clinical criteria for AIDS), suffering from chronic diarrhea defined as at least three attacks daily for a minimum of one month, were given daily doses of 10 g BC concentrated for Ig for 10 days. All participants had negative stool cultures for microbial pathogens with the exception of Cryptosporidium, although persons testing positive for this organism were allowed to participate in the trial. Seven of the participants were positive for Cryptosporidia and 18 were negative for diarrhea-causing organisms. All patients had previously received treatment with 500 mg ciprofloxacin twice daily for at least five days without success. In the 18 subjects with negative stool culture, complete remission of diarrhea occurred in seven cases (39%) and a reduction of 50 percent or more in frequency of diarrhea occurred in an additional four cases (22%). Six of the seven persons with complete remission remained diarrhea-free during the four-week follow-up period. The seven non-responders received double the dose of BC (10 g twice daily) for an additional 10 days, resulting in complete remission and a reduction of 50 percent or more in frequency of diarrhea in an additional three cases. Total response over both time periods and dose regimens in the persons with negative stool cultures was:

Complete Remission of Diarrhea
– 8 of 18 cases
Partial Remission
(50 percent or more reduction in frequency) – 7 of 18 cases
Non-responders – 3 of 18 cases

In the persons with positive stool culture for Cryptosporidia, three experienced complete remission and two had partial remission; two persons were judged as non-responders to the intervention. The three individuals with complete remission remained diarrhea-free during the four-week follow-up period. Stool frequency in the seven cases decreased from an average of 9.4 daily to 3.7 daily by the end of the 10-day intervention.[16]

Infectious Disease: Prophylaxis and Treatment

The use of BC as prophylaxis or treatment for infectious disease relates to the historical concept of "immune milk" being capable of transferring passive immunity. This concept dates back to at least the 1950s.[29,30] Building on advances in scientific understanding of the chemical structure and functions of Ig that occurred throughout the 1960s and 1970s, research in the 1980s and 1990s examined the role of BC as prevention or treatment for enteropathogenic microbes. The majority of research on either prophylaxis or treatment of infectious disease with BC has been conducted on HBC products created to have higher antibody titers against the specific microbe than would typically be found in BC. The control groups have

occasionally received BC as a placebo intervention in some trials, allowing for some degree of comparison. Currently, some degree of efficacy in either prophylaxis or treatment has been demonstrated against Cryptosporidia, *H. pylori*, rotavirus, and Shigella, while no positive effects have been seen against cholera.

Vibrio cholerae

Two trials have been conducted to investigate the effect of specific HBC preparations with Ig against cholera toxin in an attempt to alter the course of cholera infection. In both trials HBC was produced by immunizing cows with cholera toxin, resulting in a preparation containing 2.6-4.4 percent of the total IgG1 content as specific anti-cholera toxin Ig. Additional processing to concentrate the anti-cholera Ig was undertaken to ensure that 2 g per dose of specific Ig could be delivered. In both trials all patients received standard rehydration therapy.

In the first trial, 45 patients with stool samples positive for *Vibrio cholerae* and with profuse watery diarrhea of less than 24 hours duration received the HBC preparation, BC prepared from non-immunized cows, or water. The different active preparations provided 2 g anti-cholera toxin Ig (in the HBC group) or 2 g Ig with no specific activity against cholera toxin (in the non-immunized BC group). Two doses were provided at eight-hour intervals; the control group received water only. There was no evidence of a treatment effect of either the HBC preparation or the BC collected from non-immunized cows.

In the second trial, 20 patients with stool samples positive for *Vibrio cholerae* and with profuse watery diarrhea of less than 24 hours duration received in a double-blind fashion HBC preparation, BC prepared from non-immunized cows, or water. The HBC and the BC from non-immunized cows contained 2 g anti-cholera toxin Ig or 2 g Ig with no specific activity against cholera toxin, respectively. Participants received eight doses at two-hour intervals. The control group received water only. All patients received two 500 mg doses of tetracycline. No treatment effect was observed with either the HBC preparation or the BC collected from non-immunized cows.[31]

Cryptosporidiosis

As mentioned above, the literature reports several cases of the effective treatment of Cryptosporidia-induced diarrhea with elimination of stool oocysts using HBC collected from cows immunized with Cryptosporidia antigens. In most cases, patients were immune-compromised and had chronic diarrhea that had not responded to conventional treatment. In several cases, subsequent to treatment with HBC preparations, resolution of diarrhea occurred within 3-10 days and stools were no longer positive for oocysts.[24-28] BC from non-immunized cows has also appeared to be beneficial in eliminating oocysts and altering the clinical course of infection. Current evidence does not support a role of HBC in prophylaxis against infection.

Helicobacter pylori

Encouraging results have been observed with respect to decreasing the severity of gastric inflammation and symptoms; however, total eradication of *Helicobacter pylori* appears to be highly unlikely based on preliminary evidence. No data currently exists to determine the role of BC or HBC as prophylaxis against infection.

Daily doses of 20 g HBC concentrated for anti-*H. pylori* bovine Ig were given to nine adults with gastritis for 3-4 weeks. While treatment reduced the severity of symptoms and inflammation, the organism was eradicated in only one subject.[32]

Daily doses of 12 g HBC concentrated for anti-*H. pylori* bovine Ig were given to 20 children positive for *H. pylori* for 3-4 weeks. While the severity of symptoms and rate of colonization were reduced, the organism was not eradicated from any of the children.[33] Twenty-four children (below the age of five) positive for *H. pylori* were randomized to receive either 1 g HBC daily or the same amount of BC from non-immunized cows for 30 days. Neither HBC nor BC from non-immunized cows was able to successfully eradicate *H. pylori* as assessed by the C-urea breath test.[34]

Rotavirus

Evidence suggests specific HBC preparations might be effective for both prevention and treatment of rotavirus. In existing trials, HBC were produced to have high neutralizing titers of rotavirus Ig against the four human rotavirus serotypes. The existing evidence suggests this type of HBC preparation might offer prophylaxis against infection and promote more rapid recovery in persons already infected with rotavirus. Available evidence does not support a role for BC collected from non-immunized cows in prophylaxis or treatment of rotavirus.

One hundred-twenty children aged 3-15 months who had previously been admitted to a hospital for a range of health challenges received either HBC or infant formula as a placebo. The dose administered was 50 mL daily for 10 days with a follow-up period of 14 days. Complete protection against rotavirus infection occurred in the children consuming HBC; the rate of infection in children receiving placebo was 13.8 percent.[9]

Sixty-eight children aged 5-24 months with acute watery diarrhea of less than three days duration and a positive stool test for rotavirus were randomized to receive either 100 mL HBC three times daily or a similar amount of BC collected from non-immunized cows. This dose provided 10 g Ig daily. The HBC and BC used in this trial from both the immunized and non-immunized cows were collected during the first two days post-parturition. A 22-percent reduction in duration of diarrhea was observed in participants receiving HBC, the end result being resolution of diarrhea occurring an average of 16 hours sooner in the active treatment group. Within 48 hours after commencing HBC, diarrhea had resolved in 50 percent of children. Comparatively, at the same time post-intervention, nearly 100 percent of children receiving BC from non-immunized cows still had diarrhea. Total stool output was also reduced by 29 percent in participants receiving the HBC treatment.[35]

Eighty children age 4-24 months with acute diarrhea secondary to rotavirus infection were randomly assigned to receive either HBC or milk powder placebo. In all cases, diarrhea had been ongoing for less than 48 hours. Children received either 10 g HBC (containing 3.6 g of antirotavirus Ig) daily in four divided doses or milk placebo for four days. A significant reduction in daily stool frequency, cumulative four-day stool frequency, and total duration of diarrhea was observed in children receiving HBC. By the fourth day, diarrhea had completely resolved in 33 children receiving HBC compared with 21 in the placebo group. While 50 percent of children who received placebo continued to have rotavirus in their stools on the fourth day, rotavirus was no longer detectable in the stool of 95 percent of those receiving the active treatment. Clearance of rotavirus from the stool was also earlier in the HBC group compared with the placebo group (mean day, 1.5 versus 2.9, respectively). Children receiving the active treatment consumed significantly less oral rehydration solution (ORS) on days 2 and 3, and their total intake of the ORS over the four-day trial period was significantly less than the placebo group.[10]

Shigellosis

Current evidence suggests HBC produced to contain a high neutralizing titer against *Shigella sp.* might have a role in prevention of infection; however, as an intervention in existing infection, HBC and BC were equally effective.

Two different lots of HBC concentrated for Ig were produced by immunizing pregnant cows against *Shigella flexneri*. Injection number and frequency were altered to produce one lot with a higher antibody titer (1:40,960) against *S. flexneri* 2a lipopolysaccharide (LPS) and one lot with a lower antibody titer (1:2,560). The control BC preparation used in the study contained an antibody titer against this organism of 1:40. Participants ingested 10 g three times daily of the concentrates for seven days and were then given an oral challenge consisting of *S. flexneri* 2a strain 2457T followed by an additional 10 g dose of the preparations. None of the 10 participants receiving the high antibody titer HBC developed symptoms of acute illness, while three of the 11 participants receiving the HBC with a low antibody titer and five of 11 subjects receiving the control BC preparation developed symptoms of acute illness.

Table 3. *Changes in Disability Scores in MS Patients Receiving two Different HBC and a BC Preparation*

	MS Patients Receiving HBC with High NT Titer to Measles Virus	MS Patients Receiving HBC with Low NT Titer to Measles Virus	MS Patients Receiving BC Rated as Negative for NT Titer to Measles Virus
Improved Cases (as assessed by changes in Disability Scores)	5	5	0
Unchanged Cases (as assessed by changes in Disability Scores)	2	3	2
Worsened Cases (as assessed by changes in Disability Scores)	0	0	3

Adapted From: Ebina T, Sato A, Umezu K, et al. Treatment of multiple sclerosis with anti-measles cow colostrum. *Med Microbiol Immunol (Berl)* 1984;173:87-93.

The results strongly suggest a dose-response effect of HBC with respect to specific Ig for prevention of *S. flexneri* infection.[36]

HBC was produced to have a high neutralizing titer against *Shigella dysenteriae* type I by intramuscular and intramammary immunization with a vaccine containing *S. dysenteriae* type I organism to stimulate the immune systems of pregnant cows. Sixty-nine children aged 1-12 years with a history of bloody mucoid diarrhea for less than five days and a positive stool specimen for *S. dysenteriae* type I antigen were randomized to receive either HBC (100 mL three times daily) or BC collected from non-vaccinated cows (100 mL three times daily). All children enrolled also received pivmecillinam four times daily for five days. While duration of some symptoms was slightly shorter and 57-percent fewer children had a positive stool culture on day 5 in the group receiving HBC, overall clinical and bacteriological responses did not reach statistical significance between groups.[18]

Multiple Sclerosis

Preliminary evidence suggests a benefit of HBC from cows immunized with the Schwarz strain of measles virus in persons with multiple sclerosis (MS). Currently no available evidence supports a role for BC collected from cows not previously immunized with this virus.

Three different oral preparations (two of which would be considered HBC) were administered to 20 patients with MS for 30 days at a dose of 100 mL. The preparations were classified based on antibody neutralization (NT) titer to the measles virus as high (512-5120), low (8-32), or negative (< 8). Changes in disability scores from baseline to the end of treatment were assessed (Table 3). Disability scores improved in five of seven participants receiving the high NT HBC preparation and in five of eight participants receiving the low NT HBC preparation. Of the five participants receiving the BC negative for NT against measles

virus, disability scores were unchanged in two and worsened in three. The improvements observed in participants receiving the high and low NT HBC preparations were statistically significant.[37]

NSAID-Induced GI Inflammation and Permeability

BC are rich sources of various growth factors. While the concentration of the growth factors present has been incompletely defined, IGF I and II, TGF-β, and epidermal growth factor (EGF) have been identified in BC. Since these growth factors are capable of stimulating growth and repair processes within the gastrointestinal tract (GI), two studies have been conducted to determine what effect, if any, dietary supplementation might have on non-steroidal anti-inflammatory drug (NSAID)-induced GI inflammation and permeability. BC utilized in the two trials contained approximately 43 g/L protein content (primarily consisting of Ig) and the following growth factor profile (values are approximations): IGF-I and II 2 mg/L, TGF-β 25 μg/L, and EGF 6 μg/L. The preliminary results obtained suggest benefits for persons acutely exposed to NSAIDs; however, BC did not appear to provide any GI benefits among persons chronically utilizing NSAIDs.

In an initial study conducted in rats, supplementation with BC resulted in a dose-dependent reduction in the amount of GI damage caused by indomethacin. A milk solution used as a placebo was not effective.[38] As a result of the positive outcome, a study on the effects of BC on NSAID-induced intestinal permeability in humans was conducted. A milk whey solution with similar protein content but lacking growth factors was used as a placebo. Prior to commencing the studies, the BC preparation was tested against the placebo to determine whether either had an effect on intestinal permeability. The five days of supplementation did not have an effect on baseline intestinal permeability values in persons not taking NSAIDs.[39]

In the first study, seven males, following an initial baseline permeability assessment, supplemented their diets with 125 mL BC or whey placebo three times daily for seven days. Indomethacin was introduced on days 3-7. After completing this arm of the trial, a two-week washout period was followed by a second arm of the trial in which participants receiving the active intervention were switched to the placebo, while those receiving the placebo received active treatment. Permeability increased approximately threefold in response to indomethacin in the participants taking the whey placebo while no significant increase in intestinal permeability was observed when the BC preparation was co-administered with indomethacin.[39]

In the second study, 15 persons taking NSAIDs (ibuprofen, piroxicam, voltarol, or naproxen) for at least one year were randomized to receive either 125 mL BC or placebo three times daily for seven days with a two-week washout period between study arms. Baseline permeability assessments were lower in these persons than in volunteers in the previous trial (who were not taking NSAIDs chronically). No significant effect of either the active or placebo treatment was observed.[39]

Consistent with results of the first study, short-term treatment with NSAIDs has previously been shown to increase intestinal permeability.[40] However, conflicting reports on the impact of chronic long-term use of NSAIDs on intestinal permeability exist. Struthers et al, consistent with previous observations, have reported low intestinal permeability with long-term NSAID use, while Sigthorsson et al reported an approximate two-fold increase.[41,42] Currently no explanation exists for these disparate observations. While short-term doses of NSAIDs appear to consistently increase intestinal permeability, it is possible that long-term use of NSAIDs results in an adaptation response by the small intestine, at least in certain individuals. Irrespective of the explanation, BC appear to hold promise as a dietary addition in persons beginning NSAIDs, but not for persons chronically taking NSAIDs while being free of adverse GI effects.

Table 4. *Bovine Colostrums Dosing for Specific Conditions*

APPLICATION	DAILY DOSE	STANDARDIZED TO INCLUDE
Athletic Performance Improvements	60 grams daily	75% protein with 15% IgG
Body Composition Improvements	20 grams	80% protein (Ig content not determined)
Immunodeficiency-related Diarrhea	10 grams daily	Ig content of approximately 43%, suggesting an active dose of Ig of 4.3 grams daily
Infectious Disease Prophylaxis and Treatment – Cryptosporidiosis	10 grams daily	Ig content of approximately 43%, suggesting an active dose of Ig of 4.3 grams daily
NSAID-induced GI Dysfunction	15 grams daily	Protein content of approximately 43%
Surgery	14 grams four times daily	Protein content of approximately 80% with 65% Ig

Surgery

Two trials have investigated the effect of pre-surgical consumption of BC on surgery-induced changes in physiology.[43,44] While pre-surgical consumption of BC might be useful for reducing endotoxemia in abdominal surgery, a similar impact on endotoxin levels in persons undergoing coronary bypass surgery was not seen. Pre-surgical feeding of BC might also positively impact aspects of the acute phase response, including reducing post-surgical interleukin-6 (IL-6) and C-reactive protein (CRP) levels.

In an effort to assess the impact of pre-surgical feeding of BC on aspects of the response to abdominal surgery, 40 persons scheduled for stomach or pancreatic surgery were enrolled in a randomized, placebo-controlled trial. Distribution of surgery was partial gastrectomy (n=4), total gastrectomy (n=8), and pancreatic resection (n=28). The median age of participants was 55 years. BC were collected during the first 36 hours post-parturition and concentrated to contain approximately 80-percent protein content (65 percent of which was Ig). Beginning three days pre-surgery, participants consumed four doses daily (14 g per dose) of BC or a placebo beverage with similar taste and consistency. While plasma endotoxin levels increased in both groups during surgery and remained high for several days post-surgery, suggesting endotoxin translocation from the gastrointestinal tract, participants receiving BC had a significantly decreased area under the curve. No statistically significant differences in post-surgical values of IL-6 or CRP were found between active and control groups. No statistical differences were observed between groups in post-surgical clinical course.[43]

A similar BC preparation was examined in persons undergoing coronary bypass surgery. Sixty patients received either 42 g BC daily or placebo beginning two days prior to surgery. No statistical differences were observed between groups for plasma endotoxin levels post-surgically.

Peak plasma IL-6 concentrations increased to a lower maximal level in persons receiving BC; however, differences between groups did not reach statistical significance. CRP levels of all patients peaked 48 hours after surgical procedures and were significantly lower in participants receiving the BC compared with placebo.[44]

Side Effects and Contraindications

Two studies reported occasional, minor gastrointestinal complaints, including flatulence and nausea in persons supplementing with BC;[15,16] however, the side effects did not result in discontinuation of treatment. Three studies mentioned an absence of side effects of BC or HBC.[7,37,43] In one trial in which BC or HBC were given reconstituted in water, a high percentage of participants complained about the "unattractive" taste of the beverage.[15]

Dosing

The author is not aware of any of the studied HBC products currently being available as dietary supplements, so dosing recommendations are only mentioned for conditions that benefited from BC. Since standardization of active constituents of studied products has not been consistent, it is not possible to make absolute dosing recommendations. Table 4 outlines dosages used in positive trials that might be used as guidelines.

Collection times should also be considered in determining dosing and likelihood of therapeutic effect, especially in persons with immunodeficiency-related diarrhea or infectious diseases. Under these circumstances, use of BC collected more immediately post-parturition, as opposed to over several days, might be of greater clinical benefit.

Conclusion

As a general recommendation it appears warranted to select BC products for clinical use that have specified collection times and standardized protein and Ig content; dosing should then be adjusted accordingly. Standards to consider might include: (1) collection within the first 24-hours post-parturition; (2) standardized to contain a minimum of 80-percent protein; and (3) standardized to contain a minimum of 40-percent Ig. If the BC are to be used to prevent or treat infectious processes, information on specific neutralizing titers would also be beneficial; however, commercially available products typically do not provide this information.

While the observed improvements in body composition are promising, the coefficient of variance for lean body mass assessment using DEXA has been estimated to be as great as 3.1 percent. Therefore, while the observed increase in lean body mass might have been a true increase, the possibility exists it was an artifact. The benefits in performance in elite-level athletes are also promising. In existing studies on body composition and athletic performance, whey protein concentrates have been used as placebos. Whey protein concentrates, however, cannot be considered a totally inactive placebo for purposes of influencing body composition and some aspects of exercise performance. With this selection of a placebo combined with existing positive results, the initial data suggesting an ergogenic effect of BC warrants additional investigation.

Both HBC and BC appear to be capable of eliminating cryptosporidiosis; however, supplementation does not appear to be capable of preventing infection. While positive results in Cryptosporidia-induced diarrhea have been produced in some immune-compromised individuals receiving specific HBC, the small number of patients in these case reports makes it impossible to draw any meaningful conclusions. Uncontrolled trials using BC as an intervention for diarrhea in immune-compromised individuals are promising and warrant additional controlled trials.

In persons with existing cholera infection neither HBC nor BC preparations appear to be able to alter the course of the infection. The current evidence would not warrant supplementation. In other infectious disease conditions studied to date, including *H. pylori*, rotavirus, and Shigella, specific HBC products appear to warrant additional investigation; however, there is no evidence to suggest benefit from BC collected from non-immunized cows.

Preliminary findings suggest the efficacy of orally administered anti-measles HBC in improving the condition of MS patients. Although the trial was conducted on a small number of MS patients, the positive results produced warrant additional research on this specific HBC preparation and perhaps others.

BC appear to hold promise as a dietary addition in persons beginning NSAIDS, but not for persons chronically taking NSAIDS while remaining free of adverse GI effects. It is possible that persons who do experience significant adverse GI effects from chronic NSAID use have failed to adapt appropriately and might benefit from BC. Research on bovine colostrums in this patient subpopulation appears warranted.

BC appear to produce some physiological benefits in persons undergoing surgery. Since doses used were very high, additional research is needed to establish cost benefit in those undergoing surgical procedures.

References

1. Gopal PK, Gill HS. Oligosaccharides and glycoconjugates in bovine milk and colostrum. *Br J Nutr* 2000;84:S69-S74.
2. Khan Z, Macdonald C, Wicks AC, et al. Use of the 'nutriceutical', bovine colostrum, for the treatment of distal colitis: results from an initial study. *Aliment Pharmacol Ther* 2002;16:1917-1922.
3. Pedersen AM, Andersen TL, Reibel J, et al. Oral findings in patients with primary Sjogren's syndrome and oral lichen planus – a preliminary study on the effects of bovine colostrum-containing oral hygiene products. *Clin Oral Investig* 2002;6:11-20.
4. Loimaranta V, Laine M, Soderling E, et al. Effects of bovine immune and non-immune whey preparations on the composition and pH response of human dental plaque. *Eur J Oral Sci* 1999;107:244-250.
5. Liotet CC, Kogbe O. *Treatment of Severe Eye Dryness and Problematic Eye Lesions with Enriched Bovine Colostrum Lactoserum. Lacrimal Gland, Tear Film, and Dry Eye Syndromes*. New York, NY: Plenum Press; 1995:595-599.
6. Gil A, Sanchez-Medina F. Acid-soluble nucleotides of cow's, goat's and sheep's milks, at different stages of lactation. *J Dairy Res* 1981;48:35-44.
7. Stephan W, Dichtelmuller H, Lissner R. Antibodies from colostrums in oral immunotherapy. *J Clin Chem Clin Biochem* 1990;28:19-23.
8. Hagiwara K, Kataoka S, Yamanaka H, et al. Detection of cytokines in bovine colostrum. *Vet Immunol Immunopathol* 2000;76:183-190.
9. Mach JP, Pahud JJ. Secretory IgA, a major immunoglobulin in most bovine external secretions. *J Immunol* 1971;106:552-563.
10. Davidson GP, Whyte PB, Daniels E, et al. Passive immunisation of children with bovine colostrum containing antibodies to human rotavirus. *Lancet* 1989;2:709-712.
11. Sarker SA, Casswall TH, Mahalanabis D, et al. Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum. *Pediatr Infect Dis J* 1998;17:1149-1154.
12. Okhuysen PC, Chappell CL, Crabb J, et al. Prophylactic effect of bovine anti-Cryptosporidium hyperimmune colostrum immunoglobulin in healthy volunteers challenged with *Cryptosporidium parvum*. *Clin Infect Dis* 1998;26:1324-1329.
13. Antonio J, Sanders MS, Van Gammeren D. The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women. *Nutrition* 2001;17:243-247.
14. Hilpert H, Brussow H, Mietens C, et al. Use of bovine milk concentrate containing antibody to rotavirus to treat rotavirus gastroenteritis in infants. *J Infect Dis* 1987;156:158-166.
15. Rump JA, Arndt R, Arnold A, et al. Treatment of diarrhoea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum. *Clin Investig* 1992;70:588-594.
16. Plettenberg A, Stoehr A, Stellbrink HJ, et al. A preparation from bovine colostrum in the treatment of HIV-postive patients with chronic diarrhea. *Clin Investig* 1993;71:42-45.
17. Korhonen H, Marnila P, Gill HS. Bovine milk antibodies for health. *Br J Nutr* 2000;84:S135-S146.

18. Ashraf H, Mahalanabis D, Mitra AK, et al. Hyperimmune bovine colostrum in the treatment of shigellosis in children: a double-blind, randomized, controlled trial. *Acta Paediatr* 2001;90:1373-1378.
19. Sabin AB, Fieldsteel AH. Antipoliomyelitic activity of human and bovine colostrum and milk. *Pediatrics* 1962;29:105-115.
20. Francis GL, Upton FM, Ballard FJ, et al. Insulin-like growth factors 1 and 2 in bovine colostrum. Sequences and biological activities compared with those of a potent truncated form. *Biochem J* 1988;251:95-103.
21. Mero A, Miikkulainen H, Riski J, et al. Effects of bovine colostrum supplementation on serum IGF-1, IgG, hormone, and saliva IgA during training. *J Appl Physiol* 1997;83:1144-1151.
22. Hofman Z, Smeets R, Verlaan G, et al. The effect of bovine colostrum supplementation on exercise performance in elite field hockey players. *Int J Sport Nutr Exerc Metab* 2002;12:461-469.
23. Brinkworth GD, Buckley JD, Bourdon PC, et al. Oral bovine colostrum supplementation enhances buffer capacity but not rowing performance in elite female rowers. *Int J Sport Nutr Exerc Metab* 2002;12:349-365.
24. Heaton P. Cryptosporidiosis and acute leukemia. *Arch Dis Child* 1990;65:813-814.
25. Tzipori S, Roberton D, Chapman C. Remission of diarrhoea due to cryptosporidiosis in an immunodeficient child treated with hyperimmune bovine colostrum. *Br Med J* 1986;293:1276-1277.
26. Tzipori S, Robertson D, Cooper DA, White L. Chronic cryptosporidial diarrhoea and hyperimmune cow colostrum. *Lancet* 1987;2:344-345.
27. Ungar BL, Ward DJ, Fayer R, Quinn CA. Cessation of Cryptosporidium-associated diarrhea in an acquired immunodeficiency syndrome patient after treatment with hyperimmune bovine colostrum. *Gastroenterology* 1990;98:486-489.
28. Nord J, Ma P, DiJohn D, et al. Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients. *AIDS* 1990;4:581-584.
29. Campbell B, Petersen WE. Immune milk – a historical survey. *Dairy Sci Abstr* 1963;25:345-358.
30. Lascelles AK. A review of the literature on some aspects of immune milk. *Dairy Sci Abstr* 1963;25:359-364.
31. McClead RE Jr, Butler T, Rabbani GH. Orally administered bovine colostral anti-cholera toxin antibodies: results of two clinical trials. *Am J Med* 1988;85:811-816.
32. Tarpila S, Korhonen H, Salminen S. *Immune Colostrums in the Treatment of Helicobacter Pylori Gastritis*. In: Abstract book of 24th International Dairy Congress. Melbourne, Australia; 1995:293.
33. Oona M, Rigo T, Maaroos H, et al. *Helicobacter pylori* in children with abdominal complaints: has immune colostrum some influence on gastritis? *Alpe Adria Microbiology J* 1997;6:49-57.
34. Casswall TH, Sarker SA, Albert MJ, et al. Treatment of *Helicobacter pylori* infection in infants in rural Bangladesh with oral immunoglobulins from hyperimmune bovine colostrum. *Aliment Pharmacol Ther* 1998;12:563-568.
35. Mitra AK, Mahalanabis D, Ashraf H, et al. Hyperimmune cow colostrum reduces diarrhoea due to rotavirus: a double-blind, controlled clinical trial. *Acta Paediatr* 1995;84:996-1001.
36. Tacket CO, Binion SB, Bostwick E, et al. Efficacy of bovine milk immunoglobulin concentrate in preventing illness after *Shigella flexneri* challenge. *Am J Trop Med Hyg* 1992;47:276-283.
37. Ebina T, Sato A, Umezu K, et al. Treatment of multiple sclerosis with anti-measles cow colostrum. *Med Microbiol Immunol (Berl)* 1984;173:87-93.
38. Playford RJ, Floyd DN, MacDonald CE, et al. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. *Gut* 1999;44:653-658.
39. Playford RJ, MacDonald CE, Calnan DP, et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. *Clin Sci (Lond)* 2001;100:627-633.
40. Bjarnason I, Williams P, Smethurst P, et al. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. *Gut* 1986;27:1292-1297.

41. Struthers GR, Andrews DJ, Gilson RJC, et al [no authors listed in the Medline citation]. Intestinal permeability. *Lancet* 1985;1:587-588.
42. Sigthorsson G, Tibble J, Hayllar J, et al. Intestinal permeability and inflammation in patients on NSAIDS. *Gut* 1998;43:506-511.
43. Bolke E, Jehle PM, Hausmann F, et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. *Shock* 2002;17:9-12.
44. Bolke E, Orth K, Jehle PM, et al. Enteral application of an immunoglobulin-enriched colostrum milk preparation for reducing endotoxin translocation and acute phase response in patients undergoing coronary bypass surgery – a randomized placebo-controlled pilot trial. *Wien Klin Wochenschr* 2002;114:923-928.