# The Clinical Use of Bovine Colostrum

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*Abstract*

*The nutritional value of milk is largely undisputed. Colostrum, the first milk produced by mammals after parturition, has been thoroughly studied on recent years, after confirming its superior nutritional and protective value when compared to milk. Initially, colostrum was used clinically as a vehicle for passive immunity transfer. It is now known colostrum contains cytokines and other protein compounds of very low molecular weight that can act as Biological Response Modifiers (BMRs), which intervene locally in most biological processes. This article reviews the composition and current clinical use of colostrum, and describes the use of a colostral derivative in the treatment of rheumatoid arthritis and osteoarthritis.*

## Part I: Review and Proposal

Milk has always been considered a very important food–and food source–worldwide, as it supplies important nutrients in addition to carbohydrates, proteins and fat, which together contribute to the optimal functioning of the body. Maternal milk, in comparison to formula milk, has a far superior nutritional value. Colostrum has a well acknowledged crucial value for the survival of the animal species that cannot receive immunoglobulins through the placenta.[1] In recent years, due to the favorable effects of colostrum ingestion in newborn infants and animals, there has been a growing interest in determining the composition of this naturally occurring substance and determining its clinical use, in animals and humans as well. Much has also been investigated about the composition of human colostrum, and it is interesting to note the similarity in elements and functions with those of bovine colostrum. This review will specifically address data on the contents of human and bovine colostrum that constitute the basis for their immunomodulatory capacity, the current use of colostrum, and will describe a new derivative of colostrum and its clinical use.

Human Colostrum is known to be highly immunoreactive, both in the humoral and cellular systems. In 1993, Grosvenor et al. stated "many hormones, growth factors and bioactive substances present in the maternal organism are present in colostrum and milk, often exceeding concentrations that occur in maternal plasma."[2] The presence of immunoglobulin containing neutrophils and macrophages (especially IgA, and lesser amounts of IgM and IgG), and peroxidase activity identical to serum myeloperoxidase was documented recently in human colostrum.[3,4] It is known that secretory IgA (sIgA) purified from human colostrum causes in vitro inhibition of local adherence of enteropathogenic E. coli (EPEC) to Hep-2 cells because sIgA responds to a plasmid-encoded outer membrane protein implicated as the EPEC adherence factor acting as a receptor analogue.[5] Thus, colostrum provides passive immunity for the newborn.

Until recently the presence of cytokines in colostrum was unsuspected but it has been now clarified that normally there are at least four cytokines in colostrum: initially IL-1 followed by IL-2, were determined as being part of the colostral factors that stimulate resistance to infections. IL-6, tissue necrosis factor (TNF) and biologically active gamma interferon are thought to immunostimulate the oropharyngeal and intestinal lymphoid tissues in the newborn, and contribute to the development and maturation of the immune system.[1,6,7,8,10] Other factors, like Transform-

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ing Growth Factor Beta (TGFß) are present in colostrum and milk.[9]

Colostrum of mothers of pre-term babies was found to have a higher concentration of IgA, lysozyme and lactoferrin, and higher macrophage counts when compared to that of mothers of term babies. Other substances found to have a significantly greater activity in pre-term colostrum is a phagocytosis-promoting factor, which not only increases the number of phagocytic cells, but also stimulates the phagocytic activity of the individual cell.[11] The fact that colostrum of mothers of pre-term babies shows a higher nutritional and immunological value is not surprising if we consider the greater need for protection of pre-term babies. The protective effect of breast-feeding against diarrhea has been extensively studied. It is well known that the incidence of diarrhea in third world countries is inversely related to the prevalence of breast-feeding in the community.[12,13]

**Colostrum from Animals**

Bovine colostrum contains a glucose tolerance-promoting factor, which consists of a chromium-based complex, with a molecular weight around 1500. This complex was shown to participate in glucose metabolism closely related to insulin. The authors of this study hypothesize this complex could be useful to enhance glucose metabolism in adult diabetic patients.[14] The presence of a Gonadotrophin Releasing Hormone (GRH)-related peptide, presumably synthesized in the mammary gland has also been demonstrated.[15] There is evidence of IgE transference by colostrum to calves during the first 12 weeks of life, and this is assumed to generate protection against intestinal parasites. IgG, IgA, and IgM are also present in bovine colostrum showing the capacity of neutralizing human, simian and bovine rotavirus.[16] The polymorphonuclear granulocytes (PMNs) found in colostrum show a greater phagocytic activity against at least two breeds of S. Aureus than the PMNs from peripheral blood. This was demonstrated using both the rosette and phagocytosis tests.[17] Ovine and porcine colostrum enhances intestinal protein synthesis to a greater level than the synthesis induced by milk or lactose in their respective newborns. These findings support the idea that colostrum is an important factor for tissue maturation in newborns.[18-20]

Proline-Rich-Polypeptide (PRP), a polypeptide with a clear immunomodulating activity is present in ovine colostrum. PRP acts both in vivo and in vitro, and is not species specific. PRP increases skin permeability and causes differentiation of murine thymocytes into functionally active T-cells. The effects of PRP resemble the effects of thymic hormones on autoimmunity and T-cell maturation. PRP has a molecular weight of approximately 6000. It is interesting to note that fractions with a molecular weight of approximately 1000 show the same spectrum of activity of the original molecule, apparently indicating that a three amino acid sequence is responsible for the immunological effect of the peptide.[21-23]

**Use of Bovine Colostrum in Animals**

Basically, two presentations of colostrum have been evaluated for their use in animals: normal and hyperimmune colostrum. Robinson et al. in 1993 demonstrated the protective effect of normal colostrum against specific diseases: 14 foals were divided in two groups. In the first group, six foals were fed normal colostrum. In the second group, eight animals were fed whole milk. All animals were exposed to infection. Seven of the eight animals fed with milk developed signs of sepsis, and four of them died. In the colostrum-fed group, one developed diarrhea, but none developed sepsis and none died.[24] Colostrum has been specifically hyperimmunized against bovine rotavirus, and more frequently against bovine herpes type I virus and Crypto-

sporidium parvum. The goal of these studies has been to demonstrate the efficacy of colostrum as a vehicle for passive immunity. In a study, the authors fed bovine colostrum with neutralizing antibodies against herpes virus type I to calves prior to causing infection with the same virus. The most severe affection shown by these animals consisted of small areas of subacute fibrinopurulent rhinitis, but none of the animals died. The control group was fed normal colostrum, and all the calves developed fatal multisystemic infection and died.[25] The protective effect of hyperimmune colostrum against Cryptosporidium parvum was shown in calves that had a shortened period of diarrhea[26] and a similar response was seen in mice.[27,28] Another study used IgG in powdered hyperimmune colostrum against serotype 3 rotavirus to prevent diarrhea in foals.[29]

### Use of Colostrum to Treat Diarrhea in Humans

Many studies have focused in this area, specifically about the advantages of bovine colostrum as an efficient vehicle in the process of passive immunity in immunocompetent or immunocompromised humans. In children with diarrhea caused by rotavirus, the use of bovine colostrum has been tried since the mid 1980s. An important study, reported in 1989, fed 55 children with bovine colostrum with antibodies against the four serotypes of rotavirus. The control groups, 65 children, were fed artificial formula. None from the trial group and nine from the control group developed diarrhea ($p<0.001$). Parents of children from the control group sought medical attention seven times more than those in the trial group. In 1995, children treated with hyperimmune bovine colostrum were not only protected from diarrhea, but those who were affected showed a shortened course of disease. Nevertheless, results from many studies are diverse, and in some cases there seems to be no significant response.[30-32]

The studies done in immunocompetent and immunocompromised patients with diarrhea unresponsive to conventional therapies have emphasized the effect on Cryptosporidium. In 1990 the use of hyperimmune bovine colostrum against Cryptosporidium was reported to stop a three-month diarrhea in an HIV positive patient after only 48 hours of direct duodenal infusion. A similar study reported five patients with an acceptable response, still not being a success in all patients. Plettenberg et al. reported 25 HIV patients with chronic diarrhea (7 with Cryptosporidium and 18 with no identifiable agent). They demonstrated a favorable effect in 64%, complete remission in 40% and partial remission in 24% of patients, and considered this to be an excellent response, due to their previous therapeutic failures.[33-35]

### Other Alternatives: The "New" Colostrum Derivatives

There is at least one other alternative use for new colostrum derivatives which have been separated by laboratory techniques until a concentrate of basic particles is left. These particles, although not specific, have a vital and necessary role in the immuno-modulation processes of the organism. They include interferon, TNFs and cytokines 1,2 and 6. Other cytokines of recent description (cytokines 10,12, 13,15,16) are presumably found in the resulting fractions, and it is possible to find other unsuspected elements of equal or lower molecular weight, with immunomodulatory activity of the anti-inflammatory cytokine-type as well (4,10,13,15,16). The presence of immunomodulators is very important, because their activity is evident in femtomolar concentrations.[2-7] The reasoning and questions of Professor V. Bocci, from Italy, are very valid: "Why are cytokines present in colostrum – is it because they have a role in the immunological development of the newborn? Could we use this natural therapeutic strategy in adults?"[1,36]

Following this line of thought and encouraged by the result observed in animals, in 1991 a product derived from bovine colostrum was developed through a proprietory method. Other protein separation processes were then used in 1995 to isolate and purify the protein component of bovine colostrum responsible for the inhibition of S-fimbria-mediated adhesion of Escherichia coli.[36] Since the product has no demonstrable biological activity (as of 1993), our proposed mechanism of action is the induction of cytokine synthesis by the host (i.e., a true immunomodulator), allowing the organism to recuperate or reorient its "immunologic memory" thus resulting in adequate response to autoimmune conditions. These protein particles, named "Infopeptides" by their discoverer, have been extensively used in animals, and are now being used in humans under the name of Cytolog™ (which was provided by Cellogic Corporation through its distributor Allergy Research Group.™

The initial reports in small groups of patients suggested Infopeptides are efficacious in diseases such as rheumatoid arthritis, systemic lupus erythematosus, and AIDS-related intractable diarrhea, among others.[37] The next part of this article describes a clinical trial using Infopeptides as an adjuvant for the treatment of rheumatoid arthritis, in patients who did not respond to adequately established conventional therapies.

## Part II: Use of Infopeptides as an Adjuvant Therapy for Rheumatoid Arthritis: A Clinical Trial

Rheumatoid arthritis (RA) is a disease in which autoimmunity and the cytokine network are clearly involved, and despite being the most extensively studied form of arthritis, all conventional therapeutic regimes are far from satisfactory in terms of clinical response. In 1996, Feldmann et al. (from the Mathilda and Terence Kennedy Institute of Rheumatology, London, UK), reported an open-label trial done in 1992-1993, where they attempted a new treatment for RA using a chimeric (mouse x human) monoclonal anti-TNF (antibody cA2). The treatment led to rapid improvement in every patient in all parameters of disease activity used.[38] The proposed mechanism of action of Infopeptides, the specific protein derivatives obtained from bovine colostrum, is induction of anti-inflammatory cytokine-type activity by the organism, allowing the immune system to reorient or correct its response mechanism against autoimmune disease processes. Thus, this product is expected to work as a true immunomodulator. The initial clinical observations of the effects of Infopeptides in humans demonstrated marked reductions of inflammation, edema, pain and fever, apparently regardless of cause. Severe and active RA, unresponsive to conventional therapies, was chosen as a model disease to be managed with immunomodulators. Starting in March 1996, we initiated a small clinical trial with Infopeptides (Cytolog™ on 12 patients with RA, who despite adequate conventional therapy had clinical signs of active disease. At the same time we followed up 10 patients with Osteoarthrits (OA) who had no relief on conventional therapy. Because RA and OA have different ethiologic mechanisms, we must make it clear that the inclusion of OA patients in this study was incidental.

### Method

Patients included in this trial had an established diagnosis of RA or OA, with clinical and laboratory evidence of active disease, despite adequate established conventional therapy (non-steroidal anti-inflammatory drugs (NSAIDs), chloroquine, steroids, methotrexate, azathioprine, gold salts). Patients were encouraged to comply with their conventional established treatment, and were started on Infopeptides as an adjuvant supplement. Treatment was not to be considered a failure before a three-month period. The administered dose was 5 mL orally per day, and patients were instructed

to keep the product in contact with the oral mucosa for 2-3 minutes, and then swallow it. If no clinical response was observed after four weeks, the dose would then be doubled to 5 mL two times a day. All patients were evaluated clinically when they entered the trial and had a follow-up visit every four weeks. Records of clinical changes, as well as initial X-rays, laboratory exams and photographs were taken. Patients were also encouraged to report changes, or feel confident to call in case of need. RA patients were classified according to clinical severity of the disease, using the functional capacity classification: Class I: complete remission, or full capacity to develop Daily Life Activities (DLAs); Class II: moderate restriction, but still capable of handling DLAs; Class III: marked restriction, disabled to work, needs help for self care; Class IV: severe disability, bed or wheel chair confined.

### RA Patients

Twelve patients (10 F, 2 M), with an average age of 52.5 years entered the trial. The average time of disease duration was 12.4 years. Patients were taking between one and five therapeutic drugs per day (average two drugs per day). (See Table 1, below).

### Results

After a minimum three-month follow-up, the results were outstanding. Clinical and subjective improvement (i.e., subjective and objective reduction or disappearance of pain, edema and inflammation, improvement in joint mobility and better tolerance to physical activity) was documented after two to six weeks of treatment in 10 out of 12 RA patients. Two patients were lost to follow-up. An objective reduction of inflammation and local joint edema, usually preceding reduction or disappearance of pain was observed between 7 and 35 days. The average response time was 21.3 days. Patients with longer disease courses took a longer time to respond. The dose was increased to 5 mL twice a day in five patients. In spite of being advised not to stop using their established therapies, patients decided to drop other agents on their own. At the end of the initial evaluation time, the medicine intake ranged from none to 3 drugs per day (average 1.5 drugs per pa-

Table 1. Pre-treatment evaluation in patients with RA.

| Patient | Age* | Sex | Time of disease* | Stage | NSAIDs[a] | Pds[b] | Mtx[c] | Inm[d] | Clq[e] | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| MRM | 66 | F | 6 | II | X | X | X | X | | X |
| LRDL | 26 | F | 16 | II | X | | X | | | |
| EdA | 61 | F | 20 | IV | X | X | | | | |
| AA | 52 | F | 10 | II | X | X | | | | X |
| RLdV | 48 | F | 5 | II | X | | | | X | |
| MCS+ | 38 | F | 8 | II | | | | | | |
| CA | 73 | M | 12 | III | X | X | X | | | |
| MDdV | 54 | F | 20 | III | X | X | | | | |
| RG | 52 | M | 1 | I | X | | | | | |
| AmdP | 53 | F | 7 | II | X | | | | | X |
| CM+ | 52 | F | 20 | III | X | X | | | | |
| AdI | 56 | F | 24 | IV | X | X | | | | |

a: non steroidal anti-inflammatory drugs; b: predenisone; c: methotrexate; d: Inmuran; e: chloroquine.

tient-day). Six of the nine patients using NSAIDs at the time were not using them on a regular basis; since pain severity was markedly reduced, medicine intake was not as necessary as before. The RA patients with more severe conditions (functional class III-IV) have been followed for over one year, and have shown a slow but significant improvement in joint mobility, besides the initial reduction in pain, edema and inflammation (**Table 2, Figure 1**, below). With a prolonged course of treatment, we have observed dramatic changes in functional classification. In general, patients report improved quality of life, a state of well-being, better quality of sleep, increase in appetite and a noticeable reduction of frequency and severity of relapses.

### OA Patients

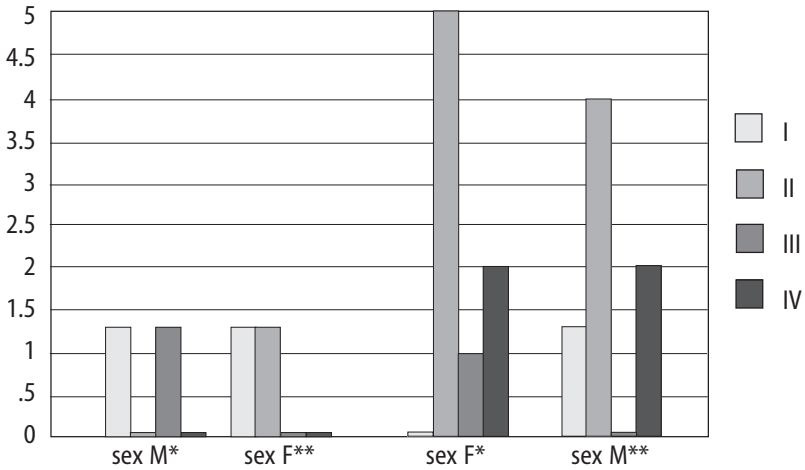
During the initial phase of the RA trial, several patients with OA asked to be included, because of the excellent results they saw on their friends or relatives. Since the Infopeptides had initially shown to be very effective in pain control regardless of cause, and because of its general safety and tolerance, we decided to initiate a parallel observation including OA patients.

Ten patients, all female, (average age 58.4 years) agreed to participate in

Table 2. Functional classification of RA patients: initial evaluation,* and after three-months of treatments**

| Functional Class | Sex M* | Sex M** | Sex F* | Sex F** |
|---|---|---|---|---|
| I | 1 | 1 | 0 | 2 |
| II | 0 | 1 | 5 | 4 |
| III | 1 | 0 | 1 | 0 |
| IV | 0 | 0 | 2 | 2 |
| Total Patients | 2 | 2 | 8 | 8 |

Figure 1. Functional classification RA patients: Initial evaluation*, and after three months of Treatment** (Data From Table 2)



theclinical trials. Duration of disease ranged from six months to 11 years, averaging 5.6 years. All patients were on a NSAID, and two had other medications when they entered the trial. OA patients were evaluated based on a patient estimated scale of pain, where 0 would be total absence of pain, and 100 the worst pain.

Nine out of 10 patients reported a significant reduction of pain, and showed clinical reduction of inflammation, between 15 and 21 days after starting the therapy. The average response time was 16 days. After the initial three-month evaluation period, only five patients were taking NSAIDs, while the others were taking the Infopeptides as their only therapy. The only patient who did not report pain reduction or relief despite showing a clinically significant reduction of local edema and heat, had severe, deforming knee damage, where surgery was advised.

## Comments

After the initial trials, we concluded that the colostrum derived product contains one or more immunomodulating agents that promote anti-inflammatory cytokine-type activity resembling the anti-inflammatory activity of cytokines 4,10,13,15,16. Longer follow-up and laboratory support data will be necessary to determine whether or not it is possible to stop, or even reverse the existent articular cartilage damage (this effect was described in vitro using cytokines 4 and 10 on mononuclear cells of RA patients).[39]

As expected from a biological response modifier, the effects of the Infopeptides are relatively non-specific, allowing the organism to recuperate normal functioning patterns. This hypothesis is supported by the good responses observed in both RA and OA. At present time, there are several other autoimmune processes that are already receiving benefit from this therapeutic alternative, with promising results.

The results of this initial clinical trial are very significant, not only because of the high level of clinical response of the whole group of patients, but also because of the sustained benefit and improvement on prolonged therapy. Its oral administration, its low cost when compared to other current experimental biological response modifiers, and the absence of side effects are remarkable as well. Nevertheless, to us, as clinicians, the most valuable aspect of this new therapeutic alternative is its profound effect on pain relief.

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