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ORIGINAL COMMUNICATION

Modulation of the immune system and the response against pathogens with bovine colostrum concentrates

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The growth, development and health conditions for children living under deprived conditions in developing countries are so adverse that immediate public health measures to reduce morbidity and improve nutrition are urgently needed. Preventing and shortening the course of diarrhoeal episodes, eliminating protozoal colonization, and balancing intestinal microflora would all contribute to these goals. The consumption by humans of part of the colostrum produced when a dairy animal gives birth is an established tradition in many traditional societies. Recent advances in food technology in industrial dairying allow for continuous availability of stabilized bovine colostrum concentrate, both natural and hyperimmunized against specific human pathogens. This is safe for the calves of the producers themselves, for laboratory animals, and generally for humans, with the caveat of the milk-allergic. Moreover, substantial amounts of orally ingested bovine colostrum concentrate survive their passage through the stomach to remain intact and active in the lower reaches of the bowel. Studies in animals, human volunteers and naturally infected humans have demonstrated a therapeutic efficacy of oral bovine colostrum with certain infections. Similarly, attempts to prevent gastrointestinal infections in animals, exposed volunteers and at-risk populations have met with limited success with specific pathogens. It is time to begin to assess the feasibility and potential effectiveness and efficiency of employing seasonal or chronic bovine colostrum feeding in populations of deprived infantile populations to reduce the rates of recurrent gastroenteritis and decrease immunostimulation to improve vitality and nutritional status in early life.
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Child health is precarious in developing countries

Research in Guatemala and other nations in Central America confronts the inescapable reality that childhood is fraught with risk of adverse health outcomes. The problems of children in developing countries are common to most locations and include: (1) poor growth (height, weight); (2) frequent infections; (3) excess mortality; and (4) rising HIV endemicity. These are related to the realities of poverty, illiteracy, entrenched cultural norms, urbanization and nutrition transition (Valdés-Ramos & Solomons, 2002).

Since children are suffering from morbidity and preventable deaths, one cannot wait for economic and social development to reform these realities. Hence, one must act directly at the level of the manifestations with the hope that making a healthier and more functional populace will assist in overall development (Berg, 1968). The interventions, however, must be accessible and appropriate. There is a complex interaction of nutrition, infection and growth: (1) prevention is better than cure; and (2) inexpensive and sustainable measurers are preferred to expensive and unavailable ones.

Reductionist *vs* holistic approaches to 'nutritional interventions'

Facing this collage of health problems afflicting underprivileged populations, it has been a tradition in public health circles to evoke nutritional deficiency and isolate a nutritional basis. The title of this issue, 'Nutrition, Infection and

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Immunity' reflects the complex interactions that were partially heralded by Scrimshaw *et al* (1959) over four decades ago, and updated with the perspective of immunology (and molecular immunobiology) which has been reviewed in this issue by Professor Chandra (2002). In most of this history — and most of this literature — the unit of interest is the individual nutrient. This is either reflected in research or in attempts to effect interventions. Thus, we have a series of theories and empirical investigations related to impacts of nutrient status on infections (Scrimshaw *et al*, 1959) or immune function (Chandra & Scrimshaw, 1980). We have interventions that look at the impact of nutrient interventions on infection and immunity in animals (Fraker, 2000) or human populations (Sommer, 1989). At this level of formulation, the approaches are inherently *reductionist*. They are based on the assumption of one nutrient — one family of effects.

I first heard the phrase 'people eat foods, not nutrients' in a lecture by the late Professor Doris Calloway at the 1974 Western Hemisphere Congress on Nutrition. This wisdom has been repeated with increasing frequency in the policy arena in recent years, but it is only rarely reflected in the academic community, as we experimental scientists prefer the reductionist methods. A *holistic* approach would be to look at the situations in which *foods* or *diet* impact on infections or immunity. The study of fermented foods containing lactic acid bacteria (probiotics) represent an exception (Naidu *et al*, 1999) to the reductionist approach, as this considers a whole *class* of foods as the modifier of immune capacity or infection risk. In a similar way, a food product — albeit obscure — *bovine colostrum*, will be considered within the paradigm of dietary modulation and modification of immune function and resistance.

Colostrum as food

Colostrum is the first milk produced by a mammal for the first 24–96 h in the postpartum period, depending on the species of mammal. In the cow, colostrum is secreted up to the sixth milking. The exposure of human populations to colostrum during human evolution has been a matter of availability and culture. Food systems were exclusively hunter-gatherer for 90% of human evolution. Forty-thousand years ago, humans domesticated certain hoofed ruminants and the nomadic, pastoralist age commenced (Cordain, 1999). Milk became available as a staple food beyond infancy. Dairying in settled agriculture began with the agriculturalist age, 10 000 y ago. Milk was consumed as the native beverage or as fermented milk, yoghurt and cheese. Table 1 illustrates some of the key biological differences between human and bovine species regarding colostrum and neonatal immunity.

Consumption of bovine colostrum has a long tradition of use as a human food in some ethnic cultures: in eastern European culture it was fed to children and pregnant and nursing mothers in the form of a pudding or custard. In modern times, colostrum from water buffalo is given as a 'health-giving' food to children and mothers in India.

Table 1 Interspecies differences

Early-life growth rate
Infant: slow weight gain to adult size (18 y)
Calf: rapid increase to adult size (3 y)
Content of colostrun
Infant: low in calcium; low in growth factors
Calf: high in calcium; high in growth factors
Passive neonatal immunity
Infant: transplacental, in uterus (3 months)
Calf: post-partum via Ig in colostrum (48 h)

Colostrum has a bitter taste, and this factor must be masked with other flavouring. Moreover, the active components of colostrum are thermolabile and it must be consumed without heating or cooking and not in combination with hot foods. Supplying colostrum in contemporary tropical nations presents a series of challenges as these settings lack refrigeration. Dried powder must be packaged to withstand the humid conditions, and safe reconstitution with microbiologically safe potable water is essential.

Colostrum for health

As with so many aspects of traditional folk medicine, the advent of medical science has substantiated a mechanistic basis for putative health-promoting effects. Early research involved the oral administration of isolated human immunoglobulins as reviewed by Ballabriga *et al* (1974/1975) and Hammarström *et al*, (1994). Later, it was realized that the placental arrangements of the cow meant that the calf's supply of immunoglobulins was supplied in the colostrum and the immunoglobulin concentrations of this liquid were orders of magnitude higher than those in human milk (Table 2). A series of modern reviews have appeared discussing the health-promoting efficacy of oral bovine colostrum (Korhonen *et al*, 2000; Hoerr & Bostwick, 2000; van Hooijdonk *et al*, 2000).

Table 2 Composition of human and bovine colostra

	Human	*Bovine*
Water	87%	78%
CHO	5.5%	3.1%
Fat	2.9%	3.6%
Protein	4.1%	14.3%
IgG	0.21 mg/ml	77 mg/ml
IgM	0.92 mg/ml	4.9 mg.ml
sIgA	13.6 mg/ml	4.4 mg/ml
Lactoferrin	+ +	+
Lysozyme	+ + + + +	+
Lactoperoxidase	+	+
Growth factors	+ + + + +	+ +

Survival of bovine colostrum during gastrointestinal transit

As milk is a food, the question of survival of active components in bovine colostrum in their passage through the digestive tract was joined. Roos *et al* (1995) labelled the immunoglobulins of bovine colostrum by feeding 15N-labelled amino acids to cows prior to parturition. By feeding these 15N-labelled bovine immunoglobulins to healthy volunteer subjects and aspirating the intestinal contents passing through the distal small intestine (ileum) through a long naso-intestinal tube, they established the survival of 19%, respectively, of the bovine IgG and IgM administered. Kelly *et al* (1997) collected whole stools of subjects who consumed a bovine immunoglobulin concentrate made hyperimmune for *Clostridium difficile*. Not only did they recover almost 4% of the total immunoglobulin administered to fasting subjects, but documented persistence of the antibody activity against the specific organism. Again, no protective influence of antacids was demonstrated.

Evidence for safety of bovine colostrum

In assessing any novel food, one must remember that lack of evidence for toxicity cannot totally be construed as conclusive evidence for safety. Within this context, the assessment of the security for humans consuming bovine colostrum begins with observations in newborn ruminants themselves. In animal husbandry, concentrates of colostrum can replace that from the maternal cow for calves, given as a single administration at 24 h of life. In laboratory rodents, single doses of non-specific and hyperimmune bovine colostrum concentrates of up to 5 g/kg, and chronic feeding over 90 days was well tolerated by rat pups (Hoerr RA personal communication, 2000). They showed normal growth and no evidence of allergenicity. Studies of human volunteers in the various intervention trials have shown no inducement of antibodies and no intact uptake of bovine immunoglobulins (Hoerr & Bostwick, 2000). All of this is supported by the cultural evidence of traditional consumption of colostrum in diverse pastoralist groups around the world.

Milk-allergic individuals can be expected to have allergic potential with bovine colostrum. Indeed, a recent serological study of milk-allergic patients found IgE cross-reactivity with colostral IgG (Lefranc-Millot *et al*, 1996).

Evidence for efficacy of bovine colostrum

Human experience with the therapeutic and prophylactic potential of bovine colostrum has ranged over a wide variety of organisms (Table 3), with varying and often inconsistent results. We can only comment on the most relevant to clinical medicine and public health.

Table 3 Range of experiences with distinct infections

Helicobacter pylori
Cryptosporidium parvum
Non-specific chronic diarrhea
Escherichia coli
Rotavirus
Vibrio cholerae
Shigella
Clostridium difficile
Candida albicans
Giardia lamblia.

Doses of bovine colostrum protein used in clinical studies have generally ranged from 3.6 to 10 g, but doses up to 50 g/day have been recorded.

Colostrum for therapeutic effects

One of the infections that has been best studied, and with evidence of successful alleviation of diarrhoeal symptoms has been bovine colostrum in rotavirus infections in infants in Bangladesh (Sarker *et al*, 1998) and Germany (Hilpert *et al*, 1987). In Germany (Miertens *et al*, 1979), in a study with infantile *Escherichia coli* infections, administration of hyperimmunized bovine colostrum ameliorated diarrhoeal episodes; in this latter study, only those infants with the specific serotypes for which the colostrum had been rendered hyperimmune had their episodes shortened.

Cryptosporidium parvum occurs naturally in cows, and occasionally causes neonatal calves' death. Bovine colostrum is richly endowed with antibodies against *C. parvum*. It was protective against cryptosporidiosis in neonatal mice (Fayer *et al*, 1990). In immunodeficiency disorders such as AIDS, chronic, persistent and debilitating cryptosporidiosis diarrhoea is totally unresponsive to any antibiotics; in various case reports and case series, an encouraging contribution of bovine colostrum to the management of this condition in immunosuppressed or immunodeficient patients has been reported (Tzipori *et al*, 1986; Ungar *et al*, 1990; Crabb, 1998).

Clostridium difficile produces mucous colitis in persons treated with multiple oral antibiotics. The use of hyperimmune anti-*C. difficile* bovine colostrum has been prepared for use as therapy to control colitis (Kelly *et al*, 1996). *Helicobacter pylori* infection is a widespread pandemic associated with peptic disease, atrophic gastritis and gastric malignancy. Its control is of high public health priority. There are *in vitro* indications that bovine colostrum inhibits the pathogenicity of *H. pylori* (Bitzan *et al*, 1998), but the clinical evidence for therapeutic eradication of infections is lacking to date. This has been tried both with and without gastric acid suppression.

Colostrum for prophylactic effects

In calves, lambs, piglets and rats, numerous efficacy trials in the veterinary literature have shown that specific hyperimmune colostra (rotavirus, *E. coli*) were protective against prospective challenges from their respective inocula. The experience with prevention of diarrhoea in human populations has been less extensive. A prospective study was done in which healthy volunteers were intentionally exposed to *Shigella flexneri* (Tacket *et al*, 1992). Regarding rotavirus, trials in Bangladesh (Mitra *et al*, 1995), and Australia (Davidson *et al*, 1989), but not in Chile (Brünser *et al*, 1992), with chronic administration of rotavirus-hyperimmune bovine colostrum have effectively reduced the incidence of diarrhoea (new episodes) in free-living infants and toddlers.

Bovine colostrum concentrate through a developing country prism

This discussion began with the explicit purpose of relieving the plight of the child at health and nutritional risk in developing countries. We must ask what particularities and peculiarities of the use of bovine colostrum exist. Feasibility, compliance and tolerance would be the watchwords. We wonder how available the bovine colostrum products would be in the region and how accessible the points of delivery to the target individuals would be. Then, when it comes to the perception and acceptance of feeding children: would it be seen as a food, as a medicine or as a nutraceutical food? Tolerance is an issue as bovine colostrum, unlike mature milk, has a bitter taste. This requires some culinary adroitness to make appealing recipes without procedures that would denature the bioactive molecules.

Qualitative cost–benefit analysis

Bovine colostrum feeding is not going to be an inexpensive measure. Even if future studies extend the findings and confirm beneficial effects with chronic consumptions, what would be the parameters of cost–benefit (efficiency) considerations that would make it viable? There are five levels of considerations: (1) that colostrum is a source of dietary protein; (2) that diarrhoeal morbidity might be lessened; (3) that protozoal carriage might be lessened; (4) that bovine colostrum might be trophic and promote child growth; and (5) that juvenile mortality rates might be lessened. Once the evidence for modelling the prediction of any population-wide benefits in these various domains is developed by ongoing and future research efforts, it will be possible to conjecture the net efficiency that interventions with colostrum feeding might offer.

The remaining hurdles for bovine colostrum

The issues about cost–benefit are speculative, and must be in a speculative framework until further developments are realized.

The science

Efficacy trials of colostrum exist on a small scale for action against specific aetiological entities. Trials are needed from the point of view of ‘polyvalent’ or ‘multi-support’ effects as a ‘functional food’ for the tropics. That means looking through the prism of well-designed randomized trials of suitably *long* duration to cover issues beyond the prevention of one or two episodes of an infection of specific aetiology. Beyond efficacy under controlled conditions, any opportunity to document the effectiveness of bovine colostrum when incorporated into programmatic interventions should not be ignored. There is a need to monitor the application of colostrum feeding in a real-life setting, and confirm any benefit and cost–benefit in a community situation

The practicalities

At the present time, cows and bovine products are under suspicion by the public and scrutiny by health authorities. Bovine spongeform encephalopathy (BSE) is the most notable, and notorious, focus that have placed cattle under the microscope of concern. Aphthous fever (foot and mouth disease), in fact, occasionally behaves as a zoonotic disease, affecting humans; we all remember the costly outbreak of this disease across Europe. Allergic phenomena are increasing worldwide, and milk protein is one of the most common food allergens.

The availability of colostrum to tropical consumers is a limiting factor. Dependence on imported sources would be sustainable at the source, but expensive after export and transport to developing countries. Bovine colostrum could be produced locally in the tropics, but the less intensive dairy production in developing countries' milk industry poses obstacles to efficient colostrum collection and local processing.

Dietary context issues in developing societies would emerge once availability issues were solved. We know that water buffalo colostrum is consumed in India, but Hindu society has a comprehensive dietary philosophy based on religious beliefs and practices. How bovine colostrum is perceived as a food and how it will be incorporated into recipes for children and other target groups in areas in which it is introduced *de novo* is unknown and requires prospective inquiry. The protective effects of bovine colostrum may be dose-dependent. It is important to determine how much of the intended dosage will be received by the intended beneficiaries in the context of emerging dietary practices.

Long-term safety issues for chronic consumption of colostrum remain to be assessed. Milk is allergenic, *per se*. Would its format as colostrum be any more allergenic? Are there as yet unknown safety issues of long-term consumption of bovine colostrum? Long-term surveillance for untoward reactions should become part of any chronic administration projects and programmes as experience moves on.

Conclusions

In Western society, food has been considered a sustenance and a source of nutrients more than a medicinal or health-modifying concept (Beaton, 1998). This is distinct from the belief-systems of developing countries, in which health and illness are related to the characteristics of food (Cosminsky & Scrimshaw, 1980). In the current wave of interest in 'functional foods', industrialized society is applying the principles well known in the tropics. For the particular health panorama of children in developing societies, however, the protective virtues of bovine colostrum might be ideal. Not all of the evidence on efficacy is in. It must be pursued as bovine colostrum feeding portends a potential entry-point to break the cycle of malnutrition and infection.

References

Ballabriga A, Hilpert H & Isliker H (1974/1975): Immunity of the infantile gastrointestinal tract and implications on modern infant feeding. In: *Nestlé Research News*, pp 25–45. Lausanne: Nestlé.

Beaton GH (1998): Recommended dietary intakes: individuals and populations. In: *Modern Nutrition in Health and Disease* ed. ME Shils, JA Olson, AC Ross & M Shike, pp 1705–1726. Philadelphia, PA: WB Saunders.

Berg A (1968): *The Nutrition Factor*. Cambridge, MA: MIT Press.

Bitzan MM, Gold BD, Philpott DJ, Huesca M, Sherman PM, Karch H, Lissner R, Lingwood CA & Karmali MA (1998): Inhibition of *Helicobacter pylori* and *Helicobacter mustelae* binding to lipid receptors by bovine colostrum. *J. Infect. Dis.* **177**, 955–961.

Brünser O, Espinoza J, Figueroa G, Araya M, Spencer E, Hilpert H, Link-Amster H & Brussow H (1992): Field trial of an infant formula containing anti-rotavirus and anti-*Escherichia coli* antibodies from hyperimmunized cows. *J. Ped. Gastroenterol. Nutr.* **15**, 63–72.

Chandra RK & Scrimshaw NW (1980): Immunocompetence in nutritional assessment. *Am. J. Clin. Nutr.* **33**, 2694–2697.

Chandra RK (2002): *Eur. J. Clin. Nutr.* **56**(Suppl 3), S73–S76.

Cordain L (1999): Cereal grains. Humanity's two-edged sword. In: *Evolutionary Aspects of Nutrition and Health: Diet, Exercise, Genetics, and Chronic Disease*. ed. AR Simopoulos, pp 19–73. Basel: Karger.

Cosminsky S & Scrimshaw M (1980): Medical pluralism on a Guatemalan plantation. *Soc. Sci. Med.* **14B**, 267–278.

Crabb JH (1998): Antibody-based immunotherapy of cryptosporidiosis. *Adv. Parasitol.* **40**, 121–149.

Davidson GP, Daniels E, Nunan H, Moore AG, Whyte PBD, Franklin K, McCloud PI & Moore DJ (1989): Passive immunization of children with bovine colostrum containing antibodies to human rotavirus. *Lancet* **2**, 709–712.

Fayer R, Guidry A & Blagburn BL (1990): Immunotherapeutic efficacy of bovine colostral immunoglobulins from a hyperimmunized cow against cryptosporidiosis in neonatal mice. *Infect. Immun.* **58**, 2962–2965.

Fraker P (2000): Impact of nutritional status on immune integrity. In: *Nutrition and Immunity: Principles and Practice* ed. ME Gershwin, JB German and CL Keen, pp 147–156. Tokawa, NJ: Humana Press.

Hammarström L, Gardulf A, Hammarström V, Janson A, Lindberg K & Smith CE (1994): Systemic and topical immunoglobulin treatment in immunocompromised patients. *Immunol. Rev.* **139**, 43–70.

Hilpert H, Brüssow H, Mierteus C, Sidoti J, Lerner L & Wercham H (1987): Use of bovine milk concentrate containing antibody to rotavirus to treat rotavirus gastroenteritus in infants. *J. Infect. Dis.* **156**, 158–166.

Hoerr RA & Bostwick E (2000): Bioactive proteins and probiotic bacteria. Modulators of nutritional health. *Nutrition* **16**, 711–714.

Kelly CP, Pothoulakis C, Vavva F, Castagliuolo I, Bostwick EF, O'Keane JC, Keates S & LaMont JT (1996): Anti-*Clostridium difficile* bovine immunoglobulin concentrate inhibits cytotoxicity and enterotoxicity of *C. difficile* toxins. *Antimicrob. Agents Chemother.* **40**, 373–379.

Kelly CP, Chetham S, Keates S, Bostwick EF, Roush AM, Castagliuolo I, LaMont JT & Pothoulakis C (1997): Survival of anti-*Clostridium difficile* bovine immunoglobulin concentrate in the human gastrointestinal tract. *Antimicrob. Agents Chemother.* **41**, 236–241.

Korhonen H, Marnila P & Gill HS (2000): Bovine milk antibodies for health. *Br. J. Nutr.* **84**(Suppl 1), S135–S146.

Lefranc-Millot C, Vercaigne-Marko D, Wal JM, Lepretre A, Peltre G, Dhulster P & Guillochon D (1996): Comparison of the IgE titers to bovine colostral G immunoglobulins and their F(ab')2 fragments in sera of patients allergic to milk. *Int. Arch. Allergy Immunol.* **110**, 156–162.

Miertens C, Keinhorst H, Hilpert H, Gerber H, Amster H & Pahud JJ (1979): Treatment of infantile *E. coli* gastroenteritis with specific bovine anti-*E. coli* milk immunoglobulins. *Eur. J. Pediatr.* **132**, 239–252.

Mitra AK, Mahalanabis D, Ashraf H, Unicomb L, Eeckels R & Tzipori S (1995): Hyperimmune cow colostrum reduces diarrhea due to rotavirus: a double-blind, controlled clinical trial. *Acta Paediatr.* **84**, 996–1001.

Naidu AS, Bidlack WR & Clemens RW (1999): Probiotic spectra of lactic acid bacteria (LAB). *Crit. Rev. Food Sci.* **39**, 1–126.

Roos N, Mahe S, Benamouzig R, Sick H & Rautureau J (1995): 15N-labeled immunoglobulins from bovine colostrum are partially resistant to digestion in human intestine. *J. Nutr.* **125**, 1238–1244.

Sarker SA, Casswall TH, Mahalanabis D, Alam NH, Albert MJ, Brussow H, Fuchs GJ & Hammerstrom L (1998): Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum. *Pediatr. Infect. Dis. J.* **17**, 1149–1154.

Scrimshaw NS, Taylor CE & Gordon JE (1959): Interaction of nutrition and infection. *Am. J. Med. Sci.* **237**, 367–403.

Sommer A (1989): New imperatives for an old vitamin (A). *J. Nutr.* **119**, 96–100.

Tacket CO, Binion SB, Bostwick E, Losonsky G, Roy MJ & Edelman R (1992): Efficacy of bovine milk immunoglobulin concentrate in preventing illness after *Shigella flexneri* challenge. *Am. J. Trop. Med. Hyg.* **17**, 276–283.

Tzipori S, Robertson D & Chapman C (1986): Remission of diarrhoea due to cryptosporidiosis in an immunodeficient child treated with hyperimmune bovine colostrum. *Br. Med. J.* **293**, 1276–1277.

Ungar BLP, Ward DJ, Fayer R & Quinn CA (1990): Cessation of cryptosporidium-associated diarrhea in an acquired immunodeficiency syndrome patient after treatment with hyperimmune bovine colostrum. *Gastroenterology* **98**, 486–489.

Valdés-Ramos R & Solomons NW (2002): Preventive nutrition: its changing context in MesoAmerica. *Nutr. Res.* **22**, 145–152.

van Hooijdonk AC, Kussendrager KD & Steijns JM (2000): In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defence. *Br. J. Nutr.* **84** (Suppl 1), S127–S134.