Developing Technologies for Prevention of Bovine Failure of Passive Transfer of Antibody (FPTA)

Elaine Hunt, *DVM, Diplomate ACVIM*
Steven D. Van Camp, *DVM, Diplomate ACT*
Sherrill Fleming, *DVM*
Food Animal and Equine Medicine
College of Veterinary Medicine
North Carolina State University
Raleigh, North Carolina

Failure of passive transfer of colostral antibody (FPTA) remains a major cause of septicemia, mortality, and economic loss in modern livestock production.[1] Calves with FPTA frequently develop enteric disease, navel infections, septic arthritis, pneumonia, or fatal colisepticemia.[2] The causes and means of avoiding FPTA have been described.[3,4] Diagnostic techniques for use in individual animal and herd problems have been summarized.[5] New technologies of immuno-supplementation are developing which may prevent the otherwise fatal septicemia in the FPTA affected calf. This article summarizes the information concerning available and emerging products.

The Developing Interest in Immuno-supplements

Use of immuno-supplements for the immunologically compromised human or calf with FPTA is a tantalizing but controversial topic. These products are derived from processed cheese whey, colostral whey or skin milk. At least five products are presently available or are being formulated using whey protein as a source of injectable, absorbable or local (enteric) bovine immunoglobulin.

Documentation of the efficacy of these immuno-supplements has lagged behind product development. In some instances, manufacturers are at a loss to define what protective agent(s) actually exists in their product. Most of these immuno-supplements have been released as nutritional supplements, a less-restrictive label than would be required were they classified as drugs or biological agents. In spite of favorable field reports and obvious consumer demand, publications of controlled challenge studies of these products are lacking. Currently, the products listed for oral administration do not claim to be adequate to protect calves against complete colostrum deprivation. Until properly tested, these products *should not be used as a total substitute for colostrum.* Although we need to approach these products cautiously, it is important to remember in these periods of experimental development and product refinement: *There is a legitimate need for these products and if they are beneficial to calves with FPTA, their development should be encouraged!*

Most of these immuno-supplements are non-specific and are targeted at the neonatal calf, foal and kid. However, the global market for human supplements with pathogen *specific* antibody is limitless, and is the real financial impetus in product development. For example: An experimental bovine globulin powder providing specific immunity against enteric pathogens such as Rotavirus, Giardia, and *Escherichia coli* is presently being evaluated experimentally in daily human consumption studies.[a] It is hoped that continuous supplementation with this type of product will supply a daily source of enteric antibody for AIDS patients suffering from chronic enteritis or for the casual vacationer concerned about contracting traveler's diarrhea. Bovine immunoglobulins have also been added to infant formula. Disease resistance in infants fed this fortified formula was similar to that of infants fed human milk, while neonates receiving infant formula alone experienced higher rates of enteric infections.[6] This technology is applicable to the cattle industry as well. A mid-Western company is presently evaluating incorporation of whey derived bovine immunoglobulins in calf milk replacer.

Cheese Whey Derivatives

Cheese whey is the most immediate and inexpensive source of bovine immunoglobulin. The protein content of liquid whey is low (0.65%) and includes beta-lactoglobulin, alpha-lactalbumin and globulin fractions.[7,8] Since total global production of cheese whey is estimated at 80 million tons/year, this still represents a large quantity of bovine immunoglobulin that is presently discarded. Large scale industrial ultrafiltration or ion exchange adsorption will make it possible to selectively concentrate bovine IgG_1, IgG_2 and lactalbumin in liquid whey, resulting in the recovery of many tons of immunoglobulins.

Colostrx® is derived from ultrafiltration of cheese whey.[b] This product looks like milk replacer and is a reconstituted

with water like a milk replacer. It is fed to the calf within 10 hours of birth. Colostrx® should not be combined with colostrum since the resulting mixture is too thick and may be excessively hyperosmotic.[8] Each Colostrx® bag contains a minimum of 24 grams (g) of bovine IgG. This product does not claim to be a total immunoglobulin substitute, and 24 g of bovine IgG represents only one-sixth to one-tenth of the oral immunoglobulin mass necessary to protect calves against septicemic colibacillosis. Electrophoretogram analysis of the mixed solution showed 87% of the total protein present was neither globulin nor albumin, and could not be identified with available laboratory standards (Table 1). Therefore, much of the product may offer little systemic benefit to the calf, or may represent an immunoglobulin aggregate which we presently cannot identify.

Table 1. Comparative Product Analysis from two Veterinary Clinical Immunology Laboratories

Product	Colostrx®	Colostrx®	CL Replacer	ID—1®
Assayed at	NCSU*	TAMU**	TAMU**	NCSU*
Bovine IgG		600 mg/dl	1040 mg%	>4000 mg%
IgG_1	832 mg%			
IgG_2	90 mg%			
Bovine IgM	52 mg%	70 mg%	70 mg%	300 mg%
Bovine IgA	150 mg%			600 mg%
Total Protein	***	17 g/dl	11.2 gram%	4.6 g/dl
Gammaglobulins gamma-1		3.87 g/dl	3.23 gram% 2.7 g/dl	4.6 g/dl
Alpha Globulin alpha-1		3.48 gram%	1.41 gram% 0.8 g/dl	
Beta Globulin beta-1		1.12 gram%	1.41 gram% 1.0 g/dl	
Albumin		8.53 g/dl	5.14 gram%	0 g/dl

*NCSU—North Carolina State University College of Veterinary Medicine, Clincial Immunology Laboratory.

**TAMU—Texas A and M University College of Veterinary Medicine. Information kindly provided by Dr. Tom Kasari.

***87% of protein was a singular fast-migrating protein that could not be identified.

Colostrum deprived calves fed Colostrx® absorb such low levels of measureable bovine immunoglobulin that they must still be considered to have FPTA. In spite of this, efficacy studies by the manufacturer suggest some protection against systemic disease does occur with Colostrx® supplementation, with mortality rates in colostrum-deprived Colostrx® supplemented calves comparable to those of colostrum-fed calves (9%).[9] No information has been released yet as to morbidity rates, specifically joint and navel infections. It must be emphasized again, however, this product is not meant to replace normal colostral ingestion, merely to augment it!!!

To explain enhanced survival in Colostrx® supplemented calves, the manufacturer postulated the presence of a new IgG_1 complex (or aggregate) that is not absorbed, but remains as a digestion resistant source of immunoglobulin in the calf's gut. This complex has been found in colostrum, milk and cheese whey, but not in serum. This complex was stable when subjected to papain and pepsin *in vitro*. A proprietary monoclonal antibody has been developed to measure the presence and activity level of the complex in company products. The aggregate will be marketed under the name Immuplex®, as a biological agent rather than as a feed supplement. In preliminary trials with Immuplex®, daily supplementation to veal calves reportedly resulted in higher average daily gains and better feed conversion than in unsupplemented calves. This was reported even when the Immuplex® supplemented calves received unmedicated milk replacer, and the control animals received milk replacer with growth promotant levels of antibiotics included.[9] Eliminating antibiotics from calf milk replacers would be beneficial in promoting a residue-free product for consumers and slowing the evolution of antibiotic resistant microbial strains in the food animal industry. If data can be produced to collaborate this information, the impact of such a product on food animal production would be substantial.

Colostrx®may prove useful in dairy herds where Bovine Leukosis Virus (BLV) infectin is widespread and eradication is desirable. Infected colostrum may be one means through which it has been postulated that calves can be infected with BLV by their dams. To prevent vertical viral infection, calves from BLV positive dams would require a complete colostrum substitute. Even if viral infection of the milk is not a concern, BLV maternal antibody titers may remain elevated for 6-8 months following colostrum ingestion, preventing early sale of valuable offspring. Although small quantities of BLV antibody are present in the whey from which Colostrx® is derived, independent tests have shown this antibody has a short half life in the calf and will not result in false positive reaction to the BLV test by the time the calf is 3 weeks of age.[10]

The authors have encountered one problem with Colostrx® when deviation from directions occurred. Excessive stable foam may develop if the product is mixed with water using a wire whisk. When this foamy product was administered via esophageal feeder (a total of two packages, the second given four hours following the first) to a large, recumbent calf lacking a sucking reflex, the calf died from bloat caused by deposition of the second administration of frothy material in the rumen. This is obviously not a problem when the calf is capable of suckling and the product is deposited in the abomasum. The additional quantity of product may also have been a factor, as no obvious problems developed following the first administration of Colostrx®.

Colostrum Derivatives

C.L. Replacer[c] is a colostrum derived milk replacer. As with colostrum, C.L. Replacer must be fed within the first few hours of life, in order to assure absorption. The manufacturer reports that colostrum deprived calves absorb 600 to 900 mg/dl of total IgG from their product. This should be a more nutritionally acceptable product than whey derivatives, since it contains milk fat plus milk protein as well as immunoglobulins. No antibiotics are added, although probiotics (*Lactobacillis acidophilus* cultures) are included to help the calf establish a non-pathogenic enteric microbial flora. This product costs about $6.00 per calf for a single administration, but must be purchased in bulk.

Analysis by the manufacturer of the reconstituted product indicates the following immunoglobulin concentrations may be expected: 1500 mg/dl of IgG; 500 mg/dl IgM; 250 mg/dl IgA. Assay of this product at a southwestern veterinary school did not result in values of IgG or IgM quite this high (see Table). If this product contained about 2000 mg/dl of total bovine immunoglobulin, one liter would provide only one tenth the necessary total immunoglobulin mass for a neonatal calf. Partial FPTA could still be a problem if C.L. Replacer is the sole source of immunoglobulin. This product will probably be limited in distribution since most colostrum produced in the US is consumed directly, and only a small proportion would be available for production of C.L. Replacer.

Another colostrum derivative is the colostrum "bolus" which has been marketed for use in goat herds wishing to raise kids free of caprine arthritis-encephalomyelitis (CAE) infection. A large calf would require a large number of these 10 gram boluses in order to provide sufficient globulin mass for protection against septicemica.

Colostrum derivatives are also used in the Impro®[d] program. This program includes guidelines for animal rearing and production, coupled with the use of several products that are colostral whey derivatives said to increase phagocyte efficacy. Cows are sensitized to specific antigens (e.g. coliforms, streptococci, etc.), and the colostrum from these cows is collected and processed by ultrafiltration. For the neonatal calf, an Impro® product called "First Food" is administered orally (9 to 10 ml). A day later, Impro®'s "Second Food" can be administered orally or by subcutaneous injection of 20 ml. Impro® has been marketed for about 18 years. It does not contain bovine immunoglobulin.[11] The product is generally sold by sales representatives directly to the farmer.

Another untrafiltrate of first-milking colostral whey is available as an oral nutritional supplement in all states but Iowa and Wisconsin, where it is available as a phenol preserved injectable. This product[e] is administered in 10 ml oral aliquots for three consecutive days. If the calf shows evidence of enteric disease, 15 to 25 ml oral aliquots can be administered. A sample of this product (ID-1) assayed at the NCSU Clinical Immunology laboratory had a surprising analysis: 4600 mg/dl total protein, 100% of which was globulin, mostly gamma-1 (2700 mg/dl) but also including beta-1 (1000 mg/dl) and alpha-1 (800 mg/dl) fractions. The product was also free of albumin (see Table). Although this product appears to be free of other milk proteins and has a much higher level of detectable immunoglobulin present than those previously mentioned (approximating the concentration of immunoglobulin in colostrum), it would still require several liters of this product to provide the entire oral immunoglobulin mass required by the calf. At manufacturer recommended dosages, less that 5g of total IgG mass would be administered to the neonatal calf. Immunoglobulins are not likely to be the only immunogenic substance in any of these products, however. Presence of the lactoferren, lymphokines, and cytokines (also found in colostrum) are thought by the manufacturer to be present in sufficient quantities in the ultrafiltrate to confer significant antibacterial activity upon the calf.

Milk Derivatives

In addition to colostrum, milk is a continuous source of low levels of bovine antibody. Antigens coated with biodegradable variable release polymers are presently being utilized to vaccinate dairy cows to produce specific antibodies against enteric pathogens. By manipulating the polymers, antigen release can occur over prolonged periods. Milk from cows vaccinated with polymer-coated antigens is thought to be high in specific antibody for prolonged periods due to the extended antigenic release. Ultrafiltration of the skim milk from these cows should result in recovery of highly concentrated, specific bovine immunolglobulin.[a] Specific antibody directed against human intestinal pathogens may soon be marketed in this country through application of this technique. As mentioned previously, a prominent calf milk-replacer company may also soon utilize this technology to produce a milk replacer with specific antibody against K99+ *E. coli* and other intestinal pathogens.

Serum Derivatives

Exogenous circulating antibodies are another source of immunoglobulins for the neonate. Lyophilized hyperimmune equine serum has been fed to foals within 5 hours of birth.[12] These lyophilized immunoglobulins obtained from equine serum were reported as a rapid means of providing immunoglobulins to foals denied adequate access to high quality mare's colostrum. Foals received 3.5 g lyophilized product/kg body weight which was reconstituted in warm water and administered by nasal gastric tube. All eight foals remained healthy although IgG levels were low by present standards (200 mg/dl to 800

mg/dl).[13] A commercial product for oral supplimentation was available for the neonatal equine deprived of a ready source of colostrum.[f] The availability of this product is presently undetermined. No such product is available for the calf.

Several questions have yet to be answered concerning all these products. Is there a loss of viability of IgG during pasteurization, lyophilization, or processing and globulin extraction from cheese whey? Are the Ig aggregates that are formed during pasteurization and processing still immunologically functional? Does processed cheese whey offer sufficient concentrations of IgM (the most important immunoglobulin for protection of the calf against neonatal colisepticemia) to be protective? Equipmentation problems make it difficult to concentrate the immunoglobulins in whey to a level necessary to provide protective IgG levels; will it be possible to develop an inexpensive product from cheese whey that contains adequate immunoglobulin concentrations? Presently we don't know the answer to these questions. We do know the exponential growth in this field of commercial immunology is only just beginning. We can expect dramatic alterations in available products, neonatal management schemes and disease prohyllaxis in the future.

[a] *Stolle Research and Development Corporation, Lebanon, Ohio 45036.*
[b] *Protein Technology, Inc. Minneapolis, Minnesota 55415.*
[c] *Cuprem, Kenesaw, Nebraska 68956.*
[d] *Pro-Ag, Inc. Minneapolis, Minnesota 55441.*
[e] *Immuno-Dynamics Inc., Perry Iowa 50220.*
[f] *EquiGam,™ Products, Inc., Tampa, Florida 33688.*

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