Abstract

Neonatal dairy animals are born agammaglobulinemic and must obtain immunoglobulins (Ig) during the period of macromolecular transport within the first 24 h of life. Maternal colostrum has been the traditional source of Ig and recommendations for provision of 2 L of colostrum in two separate feedings within the first 24 h are widespread. However, stubbornly high levels of neonatal mortality and evidence of persistence of failure of passive transfer in calves indicates that too many calves consume too little Ig from colostrum or are unable to efficiently absorb IgG. Further, recent research has suggested that methods of collecting, handling and feeding of colostrum promote the transmission of biologically and economically important diseases such as Johne’s. Several approaches to improving passive transfer and reducing risk of disease transmission have been proposed, including feeding larger amounts (4 L) of colostrum at the first feeding, pasteurization of colostrum and feeding exogenous sources of Ig. Colostrum supplements and colostrum replacers are products containing <100 or ≥100 g of IgG per dose, respectively. Sources of colostrum include lacteal secretions (milk, whey or colostrum), blood and eggs (using chicken IgY). Research suggests that the efficiency of IgG absorption varies markedly by product, method of processing and source of Ig. Immunoglobulins derived from egg and supplements containing IgG from lacteal secretions are poorly absorbed by calves. Conversely, highly concentrated IgG from blood or colostrum appear to be well absorbed. More highly concentrated products (colostrum replacers) appear to have better efficiency of absorption than supplements. Immunoglobulins can also be provided to the animal following cessation of macromolecular transport (closure) as a source of local, intestinal immunity. There is firm evidence that IgG initially absorbed from colostrum into the bloodstream is resecreted into the intestinal by crypt cells. These IgG assist in reducing the incidence and severity of many different types of gastrointestinal infections, including enteropathogenic Escherichia coli, rotavirus and Cryptosporidium parvum. Sources of IgG for oral administration following closure are similar to that of colostrum supplements; however, variation in efficacy of products depending on source is different from that of colostrum supplements and replacers. Chicken egg IgY and IgG derived from colostrum and blood all appear to be effective, but degree of effectiveness depends on the specificity of Ig against specific pathogens.
Introduction

Calves are born with a predetermined genetic potential, which may be permanently affected by management decisions implemented throughout the rearing period. Level of management has a profound effect on calf morbidity and mortality. Proper management of young stock, particularly during the neonatal period, can markedly reduce morbidity and mortality, whereas improper management leads to economic losses from increased cost of veterinary intervention, death losses, reduced growth, and suboptimal reproductive performance. In addition, poor management of young stock can reduce the lifetime productivity of the individual cow and the herd as a whole.

The most critical time in the life of the dairy replacement is during the first few days, when morbidity and mortality are greatest. The U.S. Department of Agriculture reported the inadequacy of current colostrum feeding and management practices in the U.S. The USDA reported that nearly 41% of dairy calves in a national survey had inadequate circulating concentrations of IgG at 24 h of age. Failure of passive transfer in bull calves is often greater; analysis of plasma IgG in over 1,100 calves from 3 to 8 d of age indicated that over 57% had circulating plasma IgG concentration < 10 g/L (Quigley, unpublished data). McDonough et al. (1994) also reported that 78% of 460 special-fed veal calves reared in California had adequate transfer of passive immunity.

Mortality of dairy calves born alive from birth to weaning is greater than 10% in the U.S. The most important factor associated with preweaning mortality is the consumption of colostrum and acquisition of passive immunity within the first 24 hours of birth. Approximately 50% of mortality that occurred in preweaned calves was directly related to inadequate acquisition of passive immunity.

Absorption of Immunoglobulins

Absorption of intact macromolecules across the intestinal epithelium into the neonatal circulation is possible for approximately 24 hours after the calf is born. Absorption of Ig occurs non-selectively by pinocytosis, which moves proteins into the epithelium. Proteins are transported through the cell and into the lymphatics and subsequently, to the blood. Absorption of protein appears to increase along the length of the small intestine, with the lower small intestine the site of maximal IgG absorption (Fetcher et al., 1983). Several authors have reviewed mechanisms of IgG absorption (Bush and Staley, 1980; Staley and Bush, 1985; Jochims et al., 1994).

Maturation of the small intestine, including intestinal cell turnover, increasing abomasal acidity, development of intestinal secretions, and appearance of intra-epithelial digestive vacuoles, begins shortly after birth and the ability of the intestine to absorb macromolecules without digestion is lost by about 24 hours after birth. The exact time of cessation of macromolecular transport (also known as closure) varies by immunoglobulin type but ranges from 20 to 24 hours of age.
In addition to the maturation of intestinal cells, the secretion of digestive enzymes may also contribute to lower Ig absorption by degrading Ig prior to absorption. At birth and for a limited period thereafter, the secretion of digestive enzymes remains limited to allow macromolecules such as IgG to escape digestion (Thivend et al., 1980; Guilloteau et al., 1983). By about 12 h, enzyme secretion becomes more marked, thereby reducing the ability of IgG to reach the peripheral circulation without being degraded.

**Failure of passive transfer.** Traditionally, successful transfer of passive immunity has been determined by measuring the concentration of IgG in the serum of the calf at 24 to 48 hours after birth. If serum IgG concentration exceeds some critical level, then the calf is thought to be relatively well protected against pathogens. The critical level for determining failure of passive transfer (FPT) is usually <10 g/L. Calves with <10 g/L of IgG of serum are at greater risk of disease. Of course, the concentration of serum IgG is a continuum of risk – that is, calves with <10.1 g of IgG/L of serum are not at markedly greater risk than calves with 9.9 g of IgG/L. Generally, it is well accepted that the greater the concentration of IgG in the circulation of calves at 24 to 48 hours after birth, the greater the protection against the array of pathogens to which the calf might be exposed.

Recognition of high rates of FPT in calves and difficulties in managing colostrum quality prompted researchers to find ways to provide additional IgG to improve the quality of maternal colostrum. Although nearly every farmer has been thoroughly trained as to the importance of colostrum management and early administration of high quality colostrum, the incidence of FPT and subsequent neonatal morbidity and mortality on most dairy farms remains stubbornly high. Difficulties with colostrum management include wide variation in normal colostral IgG concentration, difficulty in estimating colostral IgG concentration on the farm, presence of pathogens in colostrum and the requirement to collect and feed colostrum to calves as soon as possible after birth.

Products used as colostrum supplements were introduced into the market in the mid to late 1980’s and have become an important class of product to producers. Annually, more than 500,000 calves in the U.S. are treated with colostrum products as a means of improving success of passive transfer and reduce costs associated with neonatal disease. Numerous products have been designed for administration to neonatal calves are intended to provide a source of IgG. Other components of colostrum that contribute to an animal's resistance to disease, including leukocytes, growth factors and hormones are not formulated into products because they are difficult to obtain, process and preserve and absolute requirements are unknown.

**Colostrum Products**

The term “colostrum supplement” refers to those preparations intended to provide < 100 g of IgG/dose and are not formulated to completely replace colostrum (Quigley et al., 2002a). Supplements are formulated to be fed in conjunction with colostrum and to increase IgG concentration, which is inherently variable in colostrum. Colostral IgG
supplements may be separately categorized as those intended to provide targeted IgG (from hyperimmunized animals) and those providing non-specific IgG.

“Colostral replacers” must provide an adequate mass of IgG (>100 g of IgG/dose) and nutrients required by the calf. Energy as carbohydrate and lipid is needed to allow the calf to thermoregulate and to establish homeostasis. Digestible protein sources are required as a source of amino acids for gluconeogenesis and protein synthesis, and vitamins and minerals are essential to successful colostral replacer formulation. Vitamins and minerals – particularly those that do not cross the placenta – are needed in any product intended to replace colostrum.

Three sources of IgG may be used in colostrum supplements and replacers - lacteal secretions (colostrum and milk), blood and eggs. Each IgG source has different characteristics, advantages and limitations. Concentration of IgG in bovine milk is quite low and costs of processing to concentrate IgG are high. Collection of colostrum or milk from other species of animals (sows, mares) is not currently possible in large quantities. Collection and processing of egg IgY is directed primarily to production of antibodies against specific pathogens. Immunoglobulins derived from blood are readily available, but costs associated with high purity blood products are high.

**Colostrum Supplements.** Colostral supplements derived from whey and cow colostrum are generally produced by collection of colostrum from dairy farms. Colostrum may be directly dried (lyophilization or spray-drying) or processed to remove components (e.g., fat) prior to drying. Other products are produced by concentration of IgG in whey. Supplements are available as powders, pastes and boluses. Most modern supplement products contain 25 to 50 g of IgG/dose.

Absorption of IgG from supplements derived from lacteal secretions have generally been reported to be poor (Grongnet et al., 1986; Abel and Quigley, 1993; Zaremba et al., 1993; Garry et al., 1996; Hopkins and Quigley, 1997). Apparent efficiency of IgG absorption (AEA) from supplements derived from whey and colostrum have been reported to be very low (<7%); AEA from maternal colostrum ranges from 20 to about 35% (Quigley and Drewry, 1998). Relatively low proportion of IgG in colostrum supplements compared to total protein may affect IgG absorption and AEA. Besser et al. (1993) reported that addition of bovine serum albumin to maternal colostrum reduced serum IgG concentration in newborn calves from 9.3 to 6.9 g/L. Conversely, addition of hydrolyzed casein had no effect on IgG absorption. These data suggest that large macromolecules such as albumin may compete with IgG absorption. Davenport et al. (2000) also reported reduced IgG absorption when large amounts of non-Ig protein was added to maternal colostrum.

Preparations derived from chicken eggs have been evaluated in some studies (Erhard et al., 1995, 1997). Typically, these preparations contain IgY obtained from hyperimmunization of chickens. However, absorption of the IgY into the circulation appear to be relatively low and, therefore, these preparations may be most useful in post-closure applications (Erhard et al., 1997).
A colostrum supplement using IgG from bovine serum is currently used in the U.S. to provide absorbable IgG. Data indicated improved survival of neonatal calves this product was when fed alone or added to maternal colostrum (Arthington et al., 2000a,b; Quigley et al., 2001, 2002a). Immunoglobulin preparations derived from bovine serum have the advantage of ease of collection, available methods to fractionate the IgG and efficiency of IgG absorption similar to maternal colostrum. However, numerous countries have banned the feeding of blood proteins to ruminant animals, citing concerns regarding transmission of bovine spongiform encephalopathy. Therefore, products based on bovine serum are unavailable in many countries, including the European Union, Brazil, Japan and others.

**Colostrum Replacers.** True colostrum replacers must provide high concentrations of IgG in addition to nutrients required for establishment of homeostasis and thermoregulation within the first 24 hours of birth. Colostrum and plasma are the two sources of IgG with sufficient concentration of Ig to allow economical and efficient manufacture of colostrum replacers.

Chelack et al. (1993) fed 9 calves highly concentrated spray-dried colostrum or frozen-thawed pooled colostrum. The spray-dried product provided 126 g of Ig reconstituted in 3 L of water. Serum IgG achieved at 48 h of age were 11.6 and 10.6 g/L for calves fed colostrum and spray-dried colostrum, respectively. Calculated AEA at 10% serum volume were 45 and 47%, respectively. These data suggest that products for treatment of FPT derived from whey and/or processed colostrum can, indeed, provide sufficient IgG if they are formulated, manufactured, fed and managed properly.

**Figure 1.** Relationship between plasma IgG and total protein concentrations at 24 h of age in calves fed maternal colostrum (MC) or colostral replacer. From Quigley et al, 2002a.
Fractionation of IgG from bovine plasma is widely reported in the literature and many different techniques exist for fractionation of IgG. Several trials have been conducted to measure the absorption of IgG from calves fed IgG derived from bovine plasma (Table 1). In all cases, mean circulating IgG concentration exceeded minimal IgG concentration for successful passive transfer. However, method of fractionation and IgG concentration of the final product is important, since intake of IgG in one feeding was more efficiently absorbed than a similar mass of IgG administered in two feedings at a 12-hour interval (Hammer et al., 2004).

Method of measurement of circulating IgG may be affected by IgG source administered to neonatal calves. Quigley et al. (2002a) fed calves either maternal colostrum or a colostrum replacer containing IgG from fractionated bovine plasma and plasma IgG was measured at birth and at 24 hours of age. The relationship between plasma IgG and total protein differed by IgG source (Figure 1), indicating that indirect measurements of plasma IgG (e.g., total protein) should be used with care when non-colostrum sources of IgG are used.

Trials have evaluated calf survival and health of calves fed only colostrum replacer products. Poulsen et al. (2003) fed colostrum or a replacer product derived from bovine plasma to calves on eight dairy farms in Wisconsin and reported that the proportion of calves with FPT did not differ between calves fed maternal colostrum (n = 142) or those fed the colostrum replacer (n = 147). In addition, there were no differences in mortality or number of veterinary interventions required between groups to 14 days of age. Jones et al. (2004) fed calves (n = 79) either pooled maternal colostrum or colostrum replacer at equal IgG intakes. Concentration of plasma IgG at 24 hours of age were similar between groups and mortality, morbidity and growth to 29 days of age were unaffected by treatment.

Concentration of IgG measured on days 8, 15, 22 and 29 indicated that plasma IgG was higher in calves fed CR on days 8 and 15 (Figure 2). This may be due to the different profile of IgG isotypes in plasma derived products (approximately 50% IgG1) compared to colostrum (approximately 95% IgG1). IgG1 may be cleared from circulation more rapidly than IgG2 (Mayer et al., 2002). Quigley et al. (2001) reported similar morbidity and mortality to 60 d of age in calves (n = 160) fed either maternal colostrum or colostrum replacer. These data suggest that the potential exists to replace colostrum with highly concentrated preparations of bovine plasma.
Limitations to colostrum products. There are a number of significant limitations to the use of colostrum supplements or replacers. Firstly, the profile of antibody specificity in a colostrum product may vary markedly from the antigenic reservoir on a dairy farm. Although the calf may absorb significant IgG, they may provide little protection if they are specific for the wrong pathogens. Further, there is a biosecurity risk when using an animal protein from an unknown source. Although most colostrum products are exposed to processing steps to eliminate pathogens in the products (e.g., pasteurization, irradiation, etc.), the risk of transmission of disease may not be completely ameliorated. However, at this time, the only reliable source of large masses of polyclonal IgG required to supplement or replace colostrum are from animal sources.

Finally, the value of colostrum products have been measured exclusively by the mass of IgG contained in the product. The role of other components of colostrum – essential nutrients, growth factors, hormones, protease inhibitors, leukocytes and other essential compounds have not been considered in preparation of colostrum products. Although some products are derived from maternal colostrum, processing steps such as pasteurization and spray-drying will almost certainly reduce the activity of important colostral components such as colostral lymphocytes and heat labile proteins.

Role of IgG in intestinal immunity

The intestinal tract is the largest immunological organ in the body. Large amount of lymphoid tissue (primarily as Peyer’s patches) in the gut also contributes to the immunological capability of the intestine. These tissues are particularly important in enteric disease caused by viruses and bacteria. Traditionally, the Ig considered important in the intestine was IgA, which is secreted into the lumen of the intestine. However, other evidence suggests that IgG plays an important role in reducing the risk
of disease in animals. The two primary sources of IgG in the gut are secretion of IgG from the blood into the intestine and oral consumption of IgG.

Circulating IgG move from the circulation into the lumen of the intestine, where they can also support the intestinal immune system. Movement of IgG into the intestinal epithelium is mediated by the neonatal Fc receptor, which is found in crypt cells (Mayer et al., 2002). Besser et al. (1988a) injected $^{125}$I labeled IgG into the jugular vein of calves and monitored production of $^{125}$I (total and protein-bound) in urine and feces following the injection. The researchers concluded that a portion of IgG injected into the jugular vein moved into the intestine, where it was then excreted in the feces. In a subsequent study, Besser et al., (1988b) reported that subcutaneous injection of colostral whey containing high titers of rotavirus antibody protected colostrum deprived calves from an oral rotavirus infection. Again, the authors concluded that circulating IgG were an important source of IgG to support intestinal immunity.

Oral IgG are partially resistant to digestion (Roos et al., 1995) and can be measured in feces of animals consuming oral Ig. Oral administration of IgG has been shown to reduce morbidity and mortality of many animal species, including humans. Oral administration of bovine colostrum as a source of IgG to humans and animals as a method of reducing enteropathogenic challenge is well documented (Sarker et al., 1998). Bovine colostral IgG with specific antibody activity have been shown to reduce severity of pathogenic disease. In addition, growth factors and hormones in colostrum may improve rate of intestinal healing following insult, which can speed time of recovery and improve overall rate of bodyweight gain.

Application of egg antibodies is also widely used as a source of oral IgG (Kuroki et al., 1993; Ikemori et al., 1997; Hennig-Pauka et al., 2003). Specific egg antibodies may be produced by strategic vaccination of hens with subsequent development of eggs with high titer against the target antigen. Such a vaccination strategy can produce eggs with significant immunological activity when fed orally (Ikemori et al., 1997).

Spray-dried animal plasma is a widely used ingredient in many animal species as a source of immunologically active IgG in those countries where use of animal proteins is allowed (Quigley and Bernard, 1996; van Dijk et al., 2001; Quigley et al., 2002b; Quigley and Wolfe, 2003). Others have compared spray-dried animal plasma to antimicrobials in diets of calves (Quigley and Drew, 2000; Arthington et al., 2002; Hunt et al., 2002) in response to oral enteropathogenic challenge.

When taken collectively, these data suggest that dietary Ig may serve as a “first line of defense” against enteric pathogens, including viruses and bacteria. This “passive enteric immunity” reduces stimulation of the immune system under modern commercial animal production. The animal’s immune system is not stimulated, and as a result, pro-inflammatory cytokines are not secreted by macrophages. Cytokines secreted by macrophages affect many tissues and are responsible for liberating nutrients for use in supporting an immune response. Thus, oral Ig – either as therapy or as preventative – may be an effective means of reducing the reliance on antimicrobial therapy. As new
technologies develop to produce Ig from non-animal sources, the utility and efficacy of antibody therapy may become much more attractive and economical.

**Summary**

Current production systems in the dairy industry make the collection, processing and administration of sufficient amounts of high quality colostrum difficult to newborn calves. Additionally, the presence of transmissible disease organisms in colostrum make administration of colostrum problematic. Consequently, producers occasionally seek methods to improve the Ig content of colostrum, or look for alternatives to maternal colostrum. The current generation of products designed to supplement or replace colostrum have utility in increasing circulating IgG concentration, but much more research is needed to more completely understand the role of non-Ig components of colostrum and their effects on long-term animal production and welfare. Further, the application of oral IgG to calves post-closure has significant potential to reduce the reliance on antimicrobials. Additional development of highly concentrated sources of specific antibodies will improve animal production and welfare.

**References**


### Table 1. Plasma IgG and apparent efficiency of absorption (AEA) in calves fed colostrum supplement containing bovine Ig concentrate*

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<thead>
<tr>
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<th>Plasma IgG (g/L @ 24 h)</th>
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<tr>
<td>40</td>
<td>10.7</td>
<td>31</td>
<td>Quigley et al., 2001</td>
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<td>12</td>
<td>13.6</td>
<td>20</td>
<td>Quigley et al., 2001</td>
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<tr>
<td>39</td>
<td>14.0**</td>
<td>20</td>
<td>Jones et al., 2004</td>
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<tr>
<td>16</td>
<td>13.3</td>
<td>30</td>
<td>Quigley et al., 2002a</td>
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<tr>
<td>11</td>
<td>13.9</td>
<td></td>
<td>Quigley and Wolfe, 2002</td>
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<tr>
<td>29</td>
<td>10.8</td>
<td>30</td>
<td>Hammer et al., 2004</td>
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<tr>
<td>148</td>
<td>12.2</td>
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*Mean IgG intake = 186 g.

**Included Jersey calves.