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BOVINE NEONATAL IMMUNOLOGY

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OVERVIEW OF IMMUNOLOGIC DEVELOPMENT IN UTERO

As the fetus develops in utero, there is a progressive development of various nonimmune and immune defense mechanisms. These mechanisms can be categorized into those that are dependent on antigen recognition by antibodies or lymphocytes (specific, acquired) and those that occur independent of such recognition events (nonspecific, native). Although specific and nonspecific mechanisms can each act independently to promote host defenses, more often they act in combination and therefore provide greater protection than either system can alone. All of the various cells that provide specific and nonspecific defense mechanisms originate from the same multipotential hemopoietic stem cells.

Nonimmune defense mechanisms include effects such as enzymes in secretions, acids in the stomach, fatty acids in epithelium, and normal flora that colonize mucosal surfaces once the neonate is born. Nonimmune defenses also include the complement system and phagocytic cells (neutrophils and macrophages) that differentiate from multipotential stem cells. These cells likely contribute only minimal protection in early fetal life because they remain at their derivation sites until being released into the blood at approximately 130 days' gestation.⁴ Indeed, neutrophils contribute little to fetal inflammatory processes, and fetal macrophage function is less than that of adults with regard to assisting the immune

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response, phagocytosis, and granuloma formation. By late gestation, fetal neutrophils are capable of phagocytic activity; however, their bactericidal activity may be decreased. Near birth, the phagocytic and bactericidal capacity of neutrophils declines as a result of increased fetal cortisol levels.⁶² Bactericidal activity in the serum of the bovine fetus is present by 75 days of gestation, and measurable hemolytic complement activity has been reported at approximately 90 days of gestation.⁴⁵ Throughout gestation, however, bovine fetal complement levels are approximately half that found in adult cattle. Nonimmune defense mechanisms increase in their effectiveness throughout gestation, and although they are functional by birth, they can be suppressed by stress, malnutrition, low level infections, or exposure to toxins.

Acquired immune defenses consist of antibody, memory lymphocytes, and effector cells. As lymphocytes develop from stem cells, they are initially released into the blood, then later move to specific locations to undergo further differentiation. T lymphocytes mature in the thymus, whereas B lymphocytes undergo further maturation in the bone marrow and Peyer's patches. During the first trimester of gestation, T and B lymphocytes move from primary lymphoid organs to populate the lymph nodes, spleen, and mucosal lymphoid tissues. All this activity occurs independent of antigen exposure and stimulation.

If a fetus is exposed to a foreign antigen, whether an immunologic reaction occurs depends on what stage of development the fetus is in and the nature of the particular antigen. For example, at 120 days' gestation the bovine fetus can develop antibodies to parainfluenza-3 virus but not to other viruses or bacteria.⁴ By 190 days' gestation, the fetus can produce antibodies against bovine virus diarrhea virus; at birth it can produce antibodies against *Brucella abortus*. As fetal development continues throughout gestation, an increasing number of antigens can result in induction of an immune response. By the time a calf is born, it can respond to a wide variety of antigens but not as many as when it is fully mature.

There are at least three distinct consequences to fetal infections. First, death of the fetus can occur if the immature or inadequate defense mechanisms allow infecting organisms to replicate freely and destroy tissues. Fatal infections usually occur during early gestation, when the fetal immune system cannot mount any protective response. Second, fetal infection can result in persistently infected animals that remain infected into neonatal or adult life. Specific viruses can induce immunologic tolerance or hyporesponsiveness, resulting in little or no antibody production. Examples of such infections include border disease of sheep and bovine virus diarrhea infection of cattle. A third type of reaction can occur when fetal lymphocytes have differentiated to the point at which they can recognize protective antigens of the invading organism. In the event the fetus can recognize and react to such antigens, it may be successful in ridding itself of infection. The outcome of this form of fetal infection is dependent on similar factors that determine the fate of infections in adult animals.

IMMUNE RESPONSE OF THE NEWBORN

Upon leaving the sterile uterine environment, neonates are exposed to environmental conditions that are laden with microorganisms. Although they are capable of mounting an immune response, neonates are best characterized as being immunonaive. This inability to initiate a successful immune response is attributable to the immaturity of protective mechanisms and the time delay in the initiation and production of mechanisms necessary for the generation of humoral and cell-mediated immunity. Indeed, the initial response that is mounted is typically a primary response with a prolonged lag period and low concentrations of immunoglobulins being produced. Therefore, unless adequate maternal immunologic assistance is provided, neonates have an increased likelihood of succumbing to infections that are innocuous to adult animals. The immunologic assistance that neonates receive is through immunoglobulins and other factors present in colostrum. This topic is discussed in greater detail in following sections.

At birth, primary and secondary lymphoid organs are populated by cells that have developed independent of antigenic stimulation, and the number of circulating B lymphocytes is approximately 30% of that found in an adult. In calves, B-lymphocyte numbers reach adult levels after approximately 20 days postpartum.⁵⁶ In general, the immunoglobulins produced by these cells appear in the blood a few days after birth. For example, between 36 hours and 3 weeks of age, endogenous production of immunoglobulin G1 (IgG1) is estimated to be approximately 1 gram of IgG1 per day.¹⁸ Similar to that described in utero, calves respond to specific antigens at different times early in life. Whereas some antigens elicit an antibody response in the first days of life, others require several weeks to months to generate a response.³ The total numbers of antigens that calves respond to positively increases over time, however.

Similar to humoral immunity, local and cell-mediated immunity is deficient in calves at birth. Local gut immunity begins in the first week of life when the predominant immunoglobulin-producing cells produce immunoglobulin M for the first 3 to 5 weeks of life. Later, immunoglobulin A-producing cells appear and predominate through adulthood.²⁸ Cell-mediated immunity is deficient at birth, based on decreased reactions to phytolectins.⁴⁴ By approximately 2 weeks of age, calves reach cell-mediated immune response levels similar to that of adults.

TRANSFER OF IMMUNITY FROM THE DAM TO THE NEONATE

It has been known for more than a century that resistance to specific diseases occurs through suckling. In the early 1900s, studies indicated the direct passage of serum globulins from the dam to the neonate, by way of the mammary gland.^{17, 67} Today, it is well recognized that maternal immunoglobulins, immune cells, and various cytokines are supplied

to the neonate through the colostrum because the syndesmochorial structure of the ruminant placenta prevents prepartum transfer.

Composition and Formation of Colostrum

Immunoglobulins in Colostrum

The prepartum transfer of immunoglobulins from maternal circulation into mammary secretions, termed *colostrogenesis*, is a discrete and finite stage. In domestic ruminants, transfer begins several weeks before parturition and ceases abruptly immediately before parturition. During this brief period, up to 500 grams/week of IgG are transferred into mammary secretions.¹² Because IgG1 comprises more than 85% of the total immunoglobulin in colostrum, it is this high concentration of IgG1 that is considered the hallmark of colostrum formation.¹³ The source of colostrum immunoglobulins is the maternal circulation.¹⁴ The observation that IgG1 concentrations in colostrum are typically five to ten times higher than those of immunoglobulin G2 led to the hypothesis of a mechanism that provides specificity for the transfer of IgG1. This hypothesis has since been supported in several studies.^{12, 19, 31}

Selective transport of IgG1 into colostrum requires two separate functions.³² First, specific receptors for IgG1 must be present on the basal plasma membrane of the mammary secretory cells, positioned for capture of IgG1 in extracellular fluid. In addition, mammary secretory epithelial cells must be able to internalize and transcytose IgG1 to deliver it into the luminal secretions. Early studies demonstrated that IgG1 transfer into secretions involves an active, specific receptor-mediated process.¹⁴ Studies in cattle demonstrated that IgG1 binds an Fc-specific receptor located on the basilateral surface of alveolar epithelial cells during colostrum formation but not during established lactation.^{22, 30} These findings were confirmed through immunochemical studies that revealed depletion of staining for IgG1, but not immunoglobulin G2, in the interstitium of colostrum-forming mammary glands.³⁴ As originally hypothesized, the evidence supports a model wherein the IgG1-receptor complex is endocytosed, transported across the cell in vesicles, and released at the apical surface into colostrum.^{8, 14, 33}

Like most aspects of mammary function, it appears that colostrogenesis is under the influence of lactogenic hormones and local mechanisms within the mammary gland. Evidence suggests that the initiation of IgG1 receptor activity is temporally related to stage I lactogenesis (the enzymatic and cytologic differentiation of cells associated with limited milk secretion), and is therefore under the influence of the lactogenic hormones estrogen and progesterone.^{59, 69} Because colostrogenesis ceases before or at the onset of lactation, the hormones necessary for stage II lactogenesis (copious milk production) are likely candidates for regulating cessation of IgG1 transfer. Indeed, studies suggest that cessation of IgG1 receptor activity is under the influence of the primary lactogenic

hormone, prolactin.^{6,7} Studies have shown that the control of colostrogenesis is influenced by local regulatory mechanisms that likely act in concert with the systemic hormonal mechanisms. An example of local regulation is illustrated by the variation in immunoglobulin concentration and content that occurs between individual quarters of the same udder.^{21, 23, 40} Because one can assume that all quarters are subject to common systemic regulation, the differences must arise at the level of the glands themselves.

Nonimmunoglobulin Factors in Colostrum

Leukocytes. Until relatively recently, scientific interest regarding passive transfer of immunity focused primarily on colostrum immunoglobulins while other humoral and cellular components received much less attention. Yet for all mammalian species, colostrum contains greater than 1×10^6 cells per milliliter. The particular cell types vary according to species, the time of lactation, and various physiologic and individual conditions. An important point remains, however—neonates receive a significant number of cells through mammary secretions.

Four types of cells are found in mammary secretions, including lymphocytes, neutrophils, macrophages, and epithelial cells. Lymphocytes represent 20% to 25% of mammary secretion cells in sheep⁴⁶ and greater than 30% of cells in cow mammary secretions.⁴⁸ It is believed that these lymphocytes originate from mesenteric lymph nodes.⁴⁹ Macrophages and neutrophils predominate in the mammary secretions of most species except swine, in which epithelial cell numbers are greater.³⁵

In mammary secretions of cattle, T lymphocytes outnumber B lymphocytes at all stages of lactation. At 48 hours before and 48 hours after parturition, T lymphocytes make up 33% and 16% of mammary mononuclear cells, respectively. Within T-cell populations, an average T4/T8 ratio of 0.83 exists during this period.⁴⁸ It is now widely accepted that T cells in mammary secretions are selected cells, with phenotypes different from those found in peripheral blood.³⁷ Bovine mammary secretion T lymphocytes express predominantly the α/β T-cell receptor heterodimer (α/β TCR), whereas the γ/δ TCR makes up most T cells in peripheral blood.⁷⁰

Mammary secretion T lymphocytes have a two-times higher level of CD2 expression and five-times lower level of CD45+ expression compared with peripheral blood.⁴⁸ Depending on the phenotypic characteristics of colostrum T lymphocytes, it is likely that these cells transfer immune functions to the neonate and also secrete cytokines.³⁷ The established immunomodulating effects of mammary secretions would suggest that CD4 and CD8 cells play a role in mediation. In vitro results suggest a role of CD4 T cells through production of various cytokines. The enhanced proportions of CD8 T cells are likely to be involved in immunosuppressive properties of colostrum and milk, allowing for a more controlled activation of the neonatal immune system.³⁷

B lymphocytes make up approximately 24% of cells in bovine colos-

trum.⁴⁸ It is believed that their primary role is to synthesize dimeric immunoglobulin A, which is then excreted in the mammary secretion.

Polymorphonuclear cells isolated from mammary secretions have decreased functional capacities involving migration and phagocytosis. Because of this, it is believed that their primary role is likely devoted to defense of the mammary gland and, less so, to protection of the neonate. Interestingly, it has been hypothesized that polymorphonuclear cells, after engulfing immunoglobulin present in secretions, might protect immunoglobulins from enzymatic digestion during passage through the gastrointestinal tract of the neonate.⁵¹ Limited studies of macrophages in mammary secretions of cattle suggest that their principal role in the neonate may be to act as cytokine-producing and antigen-presenting cells.⁵⁰

Cytokines. Free cytokines are present in mammary secretions; however, only a limited amount of data concerning their activity is available. In bovine mammary secretions, interleukin-2-like activity is present 2 weeks before parturition but decreases during the last week of gestation.⁵⁸ Studies concerning tumor necrosis factor in mammary secretions are conflicting. An earlier study measuring antiviral activity, assumed to be caused by tumor necrosis factor, showed increased activity as parturition approached.⁵⁸ In a later study, however, tumor necrosis factor- α was found to be present in milk during lactation but decreased in quantity 4 to 6 weeks before parturition.⁵² Although studies have indicated that human milk lymphocytes obtained during the first week of lactation are capable of producing interferon,²⁹ it has not been found in bovine colostrum.⁵⁸ Colostrum is rich in insulin-like growth factor-I, which helps regulate growth in the newborn and may enhance early neonatal immune responses.⁴³ Finally, transforming growth factor has been found in high concentrations in bovine colostrum, although levels decrease significantly by 30 days postpartum.⁶³

Additional work needs to be done regarding free cytokines and cell-secreted cytokines and their effect on local immunity in the neonate. Techniques that detect secreted cytokines and expression of specific mRNA using labeled colostrum cells should prove useful in this endeavor.

Absorption of Colostrum

Once the dam has produced colostrum and the neonate has consumed it, an additional process must occur that involves absorption of the colostrum components by the neonate. Whereas immunoglobulin transfer from maternal circulation into the mammary gland involves an active, specific receptor-mediated process, absorption by the neonate is not selective for specific immunoglobulin isotypes, and in fact, does not appear to differentiate between most macromolecules.⁹ Specific receptors for immunoglobulins are absent in the calf's gut; rather, transport occurs through nonselective pinocytosis.⁹ Absorption is initiated by the presence of macromolecules, and the efficiency of absorption effectively

declines over approximately the first 24 hours of life.⁹ Although macromolecules do facilitate the initiation of absorption, the process of absorption is finite and declines over time irrespective of the presence of macromolecules.^{60, 61} Finally, the absorptive process appears to be saturable. Studies have shown that the efficiency of immunoglobulin absorption decreases with increasing immunoglobulin concentration in the colostrum fed.⁹ Presumably, because all macromolecules apparently compete for the same absorptive process, the mass of immunoglobulin absorbed by the calf would be inversely proportional to the concentration of nonimmunoglobulin macromolecules present in the gut lumen.

It has been established clearly that in many species, colostrum cells are able to cross the neonatal intestinal barrier.^{36, 55, 68} Although the mechanism of entry into the intestinal mucosa has not been established, maternal cells have been detected in numerous neonatal tissues, including intestinal mucosa, mesenteric lymph nodes, blood, liver, lung, and spleen. Interestingly, in neonatal pigs there is specific recognition of maternal cells. Only maternal colostrum cells can pass through the neonatal intestinal barrier, whereas maternal peripheral blood leukocytes or colostrum cells from another sow cannot.⁶⁸ Such stringent restrictions on absorption may not exist in ruminant species because maternal peripheral blood leukocytes are absorbed by lambs.⁵⁷

FATE OF PASSIVELY ACQUIRED IMMUNOGLOBULINS AND COLOSTRAL CELLS AFTER ABSORPTION BY THE NEONATE

Immunoglobulins

The half-life of colostrum-derived antibody in the neonate system is between 11.5 and 16 days.^{26, 54} Until recently, the mechanism by which IgG is cleared from the circulation was not well defined in any species. Although it was believed that the gastrointestinal tract probably accounted for at least some IgG clearance, the contribution of IgG transfer into the gut to overall IgG clearance was not known. In addition, it was unclear whether antibody activity was retained when immunoglobulins were transferred into the intestinal lumen. Studies by Besser et al¹⁰ have since determined that the major means of IgG1 clearance in calves is indeed through transfer into the intestinal lumen, where almost 70% of passively acquired IgG1 was found. Further studies showed that the passively acquired IgG1 that appears in the gastrointestinal tract, where it retains antigen-binding capabilities, is functional and helps prevent infection.^{10, 11}

Cells

Although it is well known that colostrum cells can readily cross the neonatal intestinal barrier and become distributed systemically, it has

not been determined how long these cells persist or what long-term effects they might have. This lack of information stems from the fact that the studies looking at colostrum cell absorption have been conducted over relatively short periods of time (up to 60 hours after ingestion).

EVIDENCE FOR THE PROTECTIVE ROLE OF COLOSTRAL LEUKOCYTES

There are a limited number of experimental studies that have examined the protective effects of mammary secretion leukocytes. The reference model involves protection of newborn rats from *Trichinella spiralis* infection by the administration of sensitized T lymphocytes to neonates through milk or direct per os administration.³⁷ In studies of newborn calves, colostrum lymphocytes were shown to be protective against experimental infection by rotavirus.² A significant decrease in duration of viral shedding was observed after challenge in calves receiving immune colostrum lymphocytes versus controls or calves receiving nonimmune colostrum lymphocytes. Colostrum cells have also been shown to have a protective effect against enterotoxigenic *Escherichia coli* infection in calves. Calves receiving cell-containing colostrum were shown to excrete significantly fewer bacteria compared with calves receiving cell-free colostrum.⁶² These studies, although limited in number, support the conclusion that colostrum lymphocytes play a protective role against diseases in the neonate and may reduce the course of specific diseases.

CONCEPT OF FAILURE OF PASSIVE TRANSFER

It is well accepted that neonatal ruminants depend on protection against foreign antigens through passive transfer of maternal immunity through colostrum. Colostrum is clearly a complex fluid that in addition to immunoglobulins contains various immune cells, immunoreactive substances such as cytokines, and nutritional elements. The concept of failure of passive transfer, however, has largely been used to describe situations in which the neonate does not absorb adequate levels of colostrum immunoglobulin. This narrowly focused concept is undoubtedly attributable to the fact that immunoglobulins are such a large constituent of colostrum and they have been far and above the most thoroughly studied component of colostrum. The risk of a calf contracting infectious disease, however, is unquestionably a complex equation in which serum immunoglobulin concentrations are only a single factor.

Several methods are available to measure immunoglobulin concentrations in calf blood after absorption from colostrum. These techniques, in conjunction with specific guidelines, are used to define whether a neonate has attained adequate passive transfer, or alternatively, suffers failure of passive transfer. A serum IgG1 concentration of 10 mg/mL at 48 hours of age can be used as the objective value for defining the

threshold between adequate passive transfer and failure of passive transfer.²⁰

Tests for immunoglobulin concentration vary in their speed, accuracy, and equipment required for operation. All require separation of serum as the first step. The single radial immunodiffusion and the enzyme-linked immunosorbent assay tests are the only ones that directly measure serum IgG concentration. All other tests, including zinc sulfate turbidity, sodium sulfite precipitation, whole blood glutaraldehyde coagulation, total serum solids by refractometry, and gamma-glutamyl transferase activity estimate serum IgG concentration based on total proteins for which passive transfer is statistically associated with that of IgG. Recently, several articles have been published that have fine-tuned these various testing methods to provide more accurate values for defining immunoglobulin levels in the neonate.^{25, 47, 65, 66}

Although the identification of optimum threshold values for these tests is useful, they must be kept in perspective and their use not overinterpreted. Various studies that have examined the relationship between serum immunoglobulin levels in calves and disease incidence and subsequent production have had conflicting results. Several studies have demonstrated significant increases in morbidity and mortality in calves suffering failure of passive transfer and have been reviewed.²⁰ Other studies, however, have failed to demonstrate a strong association between immunoglobulin levels and morbidity. In one study of 381 dairy calves, no statistically significant relationship was observed between plasma immunoglobulin concentrations and disease incidence or weight gain.¹⁵ In other studies involving intensive calf-rearing operations, many healthy calves with normal performance parameters had low serum immunoglobulin concentrations.^{5, 39} In another study comparing groups of calves fed high- and low-immunoglobulin concentration colostrum and calves not fed colostrum, no difference in mortality rates was observed between calves fed high- or low-immunoglobulin concentration colostrum; however, colostrum-deprived calves suffered significant mortality.⁴²

Notwithstanding the disparate results of these calf studies, some general conclusions can still be drawn. An association exists between higher IgG (or protein) levels and lower disease incidence. This association, however, appears to be more influential in herds with high disease incidence than in herds with low disease incidence. Finally, the rate of disease occurrence is a balance between a calf's ability to resist disease and the severity of disease that is challenging the calf. Although immunoglobulin concentration is one factor that contributes to disease resistance, it gives no information regarding the degree of disease challenge.

Additional factors that should be considered to assess the risk of disease occurrence include general hygiene, pathogen virulence, pathogen concentration, physical environment (temperature, humidity, wind chill, and so forth), nutritional status, and miscellaneous stresses caused by transportation, handling, surgery, and so forth. Still more factors that influence disease resistance include other nonimmunoglobulin compo-

nents of colostrum that provide immunologic activity, cellular immunity, cytokines, and locally active immunoglobulins. Unfortunately, most of these factors that can influence disease susceptibility are difficult to quantitate. Therefore, their effects on neonatal infectious disease are only superficially understood.

Finally, even if it is possible to accurately measure immunoglobulin levels in calves, doing so gives no guarantee of protection for the following reasons. First, measurement of immunoglobulin concentration does not consider if the antibodies that have been transferred will be protective against specific pathogens. Although it is possible to determine this through additional test methods, it is impractical to do so in a field setting. Next, measurement of calf serum immunoglobulin concentrations does not guarantee that the immunoglobulins will reach the appropriate site of infection in sufficient concentrations to neutralize the pathogens. Lastly, this is not meant to intimate or conclude that there is no useful purpose in measuring serum immunoglobulin levels as an indicator of passive transfer of immunity in calves. Instead, it is meant to illustrate the range of potential limitations when measuring IgG levels. It is hoped that a better understanding of these limitations will make immunoglobulin measurement even more valuable.

EFFECT OF COLOSTRUM ON NEONATAL IMMUNITY

Although colostrum is an important source of nutrition and passive immunity to calves, it also has potent immunomodulatory properties that can preclude calves from developing an active immune response to certain antigens. Passively transferred immunoglobulins can suppress neonatal immunity specifically and nonspecifically.⁴ Nonspecific inhibition is illustrated by the finding that endogenous antibody production appears sooner and reaches higher peak concentrations in colostrum-deprived calves.^{27, 38} These nonspecific inhibitory effects by colostrum may last up to 4 months.³⁸ Antigen-specific inhibition is observed when calves fed colostrum-containing, antigen-specific antibodies do not develop an antibody response when exposed to that antigen.²⁴ Interestingly, with certain antigens, an anamnestic response may develop after a second immunization, despite the fact that no antibody was measurable after the initial exposure.⁴¹

Regarding other effects on immunity, colostrum feeding reduces the number of immunoglobulin-positive cells in the lymphoid tissues of calves in an isotype-specific manner.¹ The mechanism of this phenomenon is unknown; however, it provides additional evidence that feeding colostrum can downregulate the humoral capability of calves. This may result in tolerance of maternal immunoglobulins such that the duration of passive immunity is prolonged. Colostrum-fed calves have lower peripheral blood lymphocyte blastogenic responses to T- and B-cell mitogens compared with colostrum-deprived calves.¹⁶ The immunomodulatory properties of colostrum have also been shown *in vitro*. Bovine

colostrum impairs proliferation of human T-lymphocyte lines by blocking induction via interleukin-2 and decreases antibody production by peripheral B lymphocytes.^{53, 64} Clearly, colostrum contains many immunologically active elements that may (and do) affect the immune response of calves.

An important practical consequence concerning the immunomodulatory effects of colostrum is its potential effect on vaccine responses. As a general rule, the best time to immunize a neonate is after maternal immunoglobulins have waned and the immune system is mature enough to respond adequately. As stated previously, by approximately 1 month of age cell-mediated and humoral immune response of calves should be mature enough for an adequate response. Attaining sufficiently low levels of maternally derived immunoglobulins is primarily dependent on the mass of immunoglobulin absorbed during the colostrum meal and less so on the half-life of the specific immunoglobulin isotype. The isotype is less relevant because IgG1 makes up greater than 80% of the immunoglobulin in colostrum.¹⁴ With an estimated 16-day half-life of IgG1 in calves, approximately 97% of IgG1 is catabolized after 80 days of life. Practically speaking, if multiple immunizations are administered beginning at 2 to 4 months of age, adequate protection (against the specific antigens being administered) should be achieved in the young animal.

SUMMARY

The majority of early, in utero immune development occurs independent of antigen exposure. Only later during development can a fetus respond to antigens, and even then the response depends on the stage of fetal development and the nature of the antigen. At birth, the neonate is rapidly exposed to large numbers of potential pathogens. Although immunocompetent, the neonate is immunonaive and dependent on passively acquired maternal immunoglobulins, immune cells, and other substances from colostrum for protection. Neonates that suffer failure of passive transfer of maternal immunoglobulins may be at increased risk for disease; however, many other factors interact in conjunction with the level of passively acquired immunoglobulin to determine the occurrence of disease. These include, but are not limited to, management, environment, hygiene, infection pressure, virulence of organisms, and antibody specificity.

In addition to immunoglobulins, colostrum contains large numbers of immune cells and cytokines. It is thought that the primary role for the cellular component of colostrum is to interact with the development of local immunity and to modulate active immunization of the neonatal intestine. In particular, T lymphocytes are thought to transfer immune functions and secrete cytokines. Although most of the major cytokines have been identified in colostrum and milk, their biologic effects on the neonate have yet to be determined.

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