Immunology of the Bovine Neonate

Dusty W. Nagy, *DVM, MS, DACVIM, University of Illinois, Urbana, IL 61802*
Jeff W. Tyler, *DVM, PhD, DACVIM, University of Missouri, Columbia, MO 65211*

Abstract

Disease of the bovine neonate can be prevalent and devastating to the producer. The diseases common to neonates are not unique to this age group. However, many are uncommon causes of clinical disease in older animals. The importance of colostral immunoglobulin transfer in calf health is undisputed. However, the role of epithelial barrier mechanisms, cell mediated immunity, complement cascade, and the development of the calf's endogenous immunoglobulin production are often overlooked. Differential maturation of the immune response is a major contributor to the timing of common diseases in the bovine neonate. In addition, management procedures may adversely affect some of these early protective mechanisms. Understanding the maturation of the immune system in the postpartum calf sheds light on the unique pattern of diseases seen in the bovine neonate.

Introduction

Disease of the bovine neonate can be prevalent and devastating to the producer. The diseases common to neonates are not unique to this age group. However, many are uncommon causes of clinical disease in older animals. Bovine neonates are born immunologically naïve. This period of naïveté is a transient window of opportunity for pathogens. Understanding the unique differences in immune function between the neonate and the adult animal will enable a better understanding of disease in neonatal calves.

Immunology Review

Protection from pathogens is accomplished by many mechanisms in the body. Epithelial surfaces form a barrier that prevents microorganisms from easily penetrating into the body. Adaptations of some epithelial surfaces, such as the respiratory and gastrointestinal mucosa, increase their protective functions. Mucous and ciliary action protects the respiratory tract by trapping and mechanically removing pathogens. The acidic environment of the abomasum kills many bacteria and prevents colonization of the gastrointestinal tract. The presence of normal bacterial flora also aids in protection of epithelial surfaces. These organisms compete for food and attachment sites with pathogenic bacteria, and many produce antimicrobial substances that inhibit pathogenic organisms. Once epithelial barriers are breached, innate immune functions, and adaptive immune functions if necessary, are present for protection.

The innate immune response is comprised of many different processes that attempt to protect the host from invading microorganisms. These responses are all characterized by recognition of ubiquitous pathogen molecules and a lack of immunologic memory. These include cytokine production by phagocytic cells, killing of viral and intracellular pathogens by natural killer cells, and interferon production by viral infected cells.

The inflammatory mediators produced by the phagocytic cells have many local and systemic effects. They are responsible for inducing the production of acute phase proteins and increasing body temperature. Chemokine release recruits additional leukocytes to the site of infection. Expression of endothelial adhesion molecules allows immune cells to migrate out of the vasculature to the site of infection. Local production of TNF – α results in the occlusion of small vessels. This helps prevent bacterial access to the circulation and subsequent dissemination of the infection. It also helps route pathogen laden leukocytes to the lymph and lymph nodes, which facilitates antigen presentation and the start of the adaptive immune response.

The adaptive immune response occurs when the innate mechanisms are unable to adequately suppress infection. These responses are centered on T and B lymphocytes and their participation in cell mediated and humoral immunity. CD8 T cells differentiate into cytotoxic T cells when exposed to viral antigens on the host cell surface. The cytotoxic cells can then directly kill infected host cells. CD4 T cells are exposed to processed pathogen antigens in the lymph nodes. Depending on the cytokine milieu of the lymph node, the T cells will differentiate into helper 1 cells (T_H1) or helper 2 cells (T_H2). T_H1 cells activate macrophages and induce B cells to produce opsonizing antibodies, while T_H2 cells induce antigen specific naïve B cells to produce antibody of the IgM class.

Immunoglobulins function by neutralizing, opsonizing, or by activating complement. Neutralizing antibody binds to viruses and intracellular bacteria obstructing pathogen binding sites so that they can no longer enter host cells. These types of antibodies may

also bind to and inactivate bacterial toxins. Opsonizing antibodies coat pathogen surfaces to enhance phagocytosis by leukocytes. Lastly, antibodies may activate the proteins of the complement cascade by binding to pathogen surfaces.

Colostrum Components

The ingestion and absorption of maternally derived colostral components plays a large role in the immunologic capability of the neonate. Bovine colostrum contains many substances that support immune function in the neonatal calf. Immunoglobulins are the most commonly studied molecules, but maternal derived immune cells, complement factors, lactoferrin, insulin like growth factor – 1, transforming growth factor, interleukin 2, and other soluble factors are present. The exact role and importance of many colostral factors is not well elucidated at this time.

In addition to providing immune and growth factors, colostrum also has substantial immunomodulatory action. Colostrum-deprived calves generate more endogenous immunoglobulins earlier than those that have received colostrum. It has also been noted that calves may not respond to early vaccination when they have received colostrum. Despite nonresponsiveness on first inoculation, some pathogens may still demonstrate an anamnestic response on subsequent inoculations, as has been seen with IBR vaccination.[2]

Some of the immunomodulatory actions of colostrum can be viewed as negative for the calf. It is important to remember that colostrum is an extremely complex fluid and none of these potentially negative effects can be taken as isolated events, ignoring all of the benefits of colostral ingestion.

Table 1. Functional protein classes in the complement system.[a]

Binding to antigen antibody complexes	C1q
Activating enzymes	C1r, C1s, C2b, Bb, D
Membrane binding proteins and opsonins	C4b, C3b
Peptide mediators of inflammation	C5a, C3a, C4a
Membrane attack proteins	C5b, C6, C7, C8, C9

From Janeway CA. Immunobiology.[6]

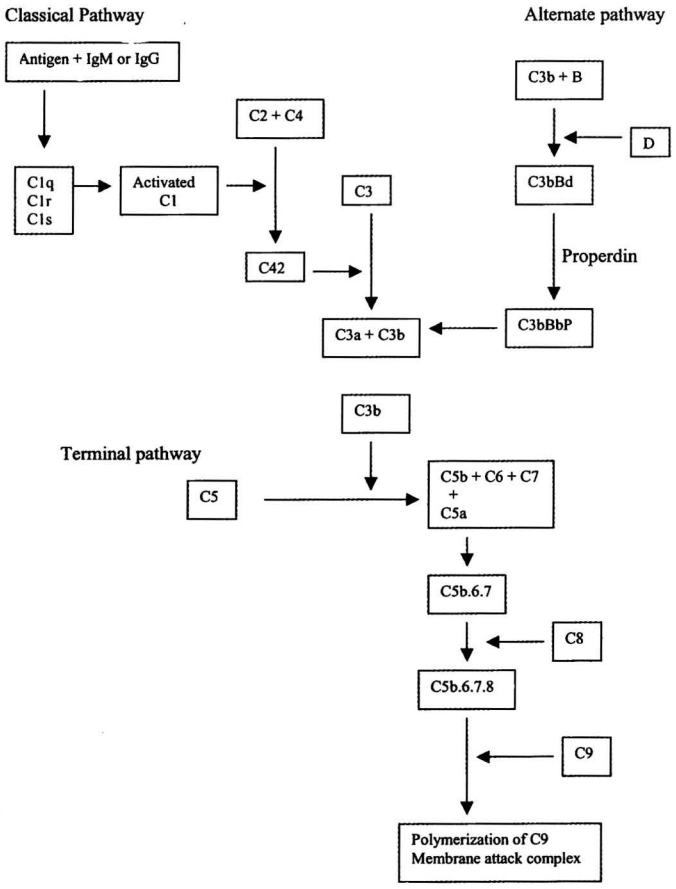

Figure 1. The complement cascade.

Ontogeny of the Immune Response

Although calves have been reported to recognize and make antibodies to complex viral antigens as early as midgestation, this should not be construed to mean the calf has an intact, fully functional immune system. Ontogeny of the immune response follows a sequential course; recognition of foreign proteins is acquired first, followed by carbohydrates, and finally lipopolysaccharides are recognized as foreign.[10] Consequently, calves are unable to recognize the lipopolysaccharide antigens of the gram-negative cell wall until they are one month of age.[13] This deficiency is noteworthy given the predominance of gram-negative pathogens in the neonatal calf.

Immunologic Naïveté

While calves are born with the ability to respond to many pathogens, they do not possess the full immunologic armor present in adult cattle. Some pathogens fail to elicit immune responses in the neonate. Low levels of immunoglobulin production, poor gastrointestinal mucosal immunity, deficiciencies in leukocyte numbers and function, and deficiencies in key complement components are also immunologically crippling for the neonatal calf.

Calves are born with minimal background exposure to pathogenic bacteria, viruses and protozoa. After being exposed there is a normal lag time between exposure and a detectable immune response. A primary immune response will generally not be observed for at least 10-14 days after exposure or immunization.

Endogenous immunoglobulin production studies in colostrum-deprived calves confirm that neonates are able to make immunoglobulins, but the concentrations produced are far lower than that of adult cattle. Immunoglobulins appear in the blood beginning at day 4 for IgM and IgA, day 8 for IgG2 and day 32 for IgG1. Adult concentrations of IgM, IgA, and IgG1 are achieved by day 128. However, IgG2 concentrations are only half of adult values at this time.[4]

Local immunity in the gastrointestinal tract is a key component in protection from enteric pathogens. While this system develops in the first week of life, the immunoglobulin profile in neonates is different from that of adult cattle. In newborns IgM is the predominant immunoglobulin present. At approximately five weeks of age the IgA secreting cells become established, and IgA becomes the predominant immunoglobulin associated with local immunity in the gut throughout adulthood.[5]

In addition to immunoglobulins, differences have been documented in lymphocyte count, T cell responses and neutrophil function. Lymphocyte concentrations are approximately one-third that of the adult animal. Adult concentrations are not achieved until calves are 20 days of age.[12] T cell responses to phytohemagglutinin are depressed until 14 days of age.[11] Neutrophil function is depressed until somewhere between 11 and 19 weeks of age.[3]

Calves are born with negligible concentrations of the third component of complement (C3). Concentrations of C3 reach adult concentrations at one month of age.[7] This relative C3 deficiency is important because C3 activation is the initial step in the activation of the common pathway. Consequentially, chemotaxis, opsonization and complement-mediated killing are probably inadequate in the neonatal calf. The absence of C3 is of further important because lipopolysaccharide portions of the gram-negative cell wall can directly activate the alternative pathway. This provides a nonspecific immune mechanism targeting gram-negative bacteria, the principal disease pathogens of neonatal calves.

Summary

It is important to recognize that many factors in the neonatal calf are present that profoundly impact the animal's ability or inability to respond to various antigens in its environment. For years the primary focus has been on immunoglobulins provided in colostrum. The role that ingestion and absorption of colostrum plays in neonatal health is undisputed. But, it is imperative to remember that all facets of the neonate's immune system are affected. The immaturities of the bovine immune system during the first weeks of life make a unique setting for disease. For this reason we often see diseases in the first weeks of life that are uncommon in older animals. Understanding the neonatal immune system will shed light on common clinical disorders of the bovine neonate.

References

1. Banks KL: Host defense in the newborn animal. *J Am Vet Med Assoc* 181:1053-1056, 1982.
2. Brar JS, Johnson DW, Muscoplat, *et al*: Maternal Immunity to infectious bovine rhinotracheitis and bovine viral diarrhea viruses: Duration and effect on vaccination in young calves. *Am J Vet Res* 39:241-244, 1978.
3. Hauser MA, Koob MD, Roth JA: Variation in neutrophil function with age in calves. *Am J Vet Res* 47:152-153, 1986
4. Husband AJ, Lascelles AK: Antibody responses to neonatal immunization in calves. *Res Vet Sci* 18:201-207, 1975.
5. Husband AJ: Ontogeny of the gut associated lymphoid system. In Butler JE (ed): *The Ruminant Immune System*. New York, Plenum Press, pp 633-647, 1980.
6. Janeway CA, Travers P, Walport M, Capra JD: Immunobiology: The immune system in health and disease, ed 4. New York, Elsevier Science.
7. Mueller R, Boothby JT, Carroll EJ, Panico L: Changes in complement values in calves during the first month of life. *Am J Vet Res* 44(5):747-750, 1983.
8. Osburn BI: Immune responsiveness of the fetus and neonate. *J Am Vet Med Assoc* 163:801-806, 1973.
9. Osburn BI, Stabenfeldt GH, Ardens AA, *et al*: Perinatal immunity in calves. *J Am Vet Med Assoc* 164:259-298, 1974.
10. Osburn BI, MacLachlan NJ, Terrell TG, *et al*: Ontogeny of the immune system. *J Am Vet Med Assoc* 181:1049-1052, 1982.
11. Rossi CR, Kiesel GK, Hudson RS: Kinetics of detection of blastogenic responses of neonatal calves inoculated *in utero* with tetanus toxoid, killed *Mycobacterium bovis*, and killed *Brucella abortus*. *Am J Vet Res* 40:576-579, 1979.
12. Senogles DR, Muscoplat CC, Paul PS, *et al*: Ontogeny of circulating B lymphocytes in calves. *Res Vet Sci* 25:34-36,1978.
13. Tyler JW, Cullor JS, Thurmond MC, *et al*: Humoral response in neonatal calves following immunization with *Escherichia coli* (strain J5): the effects of adjuvant, age, and colostral passive interference. *Vet Immunol Immunopathol* 23:333-344, 1989.