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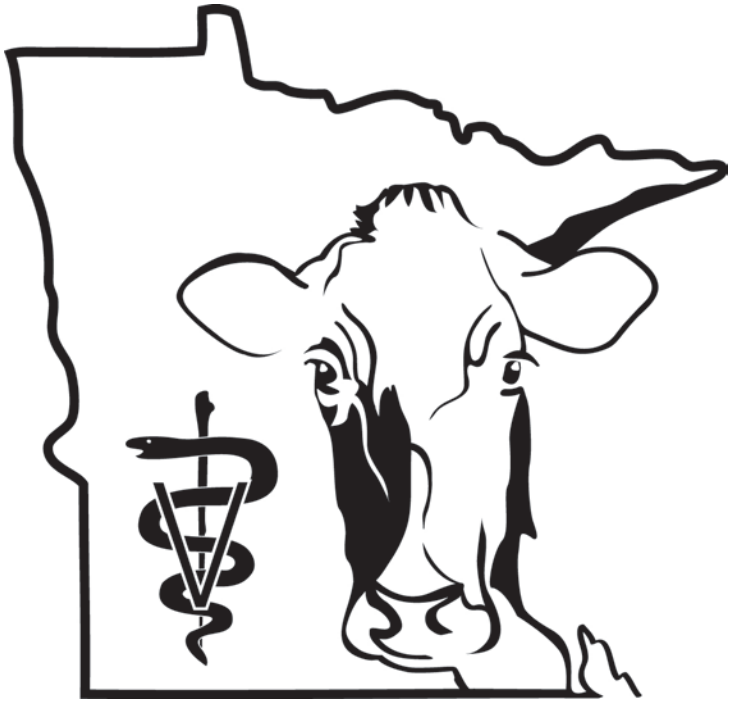

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Neonatal Immunology

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Introduction

The field of neonatal immunology is going through a revolution both in human and veterinary medicine. The advent of new and advanced methods for accessing immune status and function are being widely used to re-evaluate some of the old beliefs about the young animal's immune system. While still in its infancy, these new studies are shedding light on a mysterious and critical time in the immunologically frail newborn .

Development of the Prenatal Immune System

The immune system of all species of mammals begins development fairly early in gestation. As the fetus grows the immune system goes through many changes as cells appear and become specialized. In general, the shorter the gestation period, the less developed the immune system is at birth[1]. However, the fetus does become immunocompetent while in utero to many diseases. The best example is the ability of the bovine fetus to mount an antibody response to bovine viral diarrhea virus. For these types of diseases precolostral titers from the neonate can be used for diagnostic determination of fetal exposures. The primordial thymus can be seen in both fetal lambs and calves between day 27-30 as an epithelial chord[2,3]. As a percentage of body weight, the thymus reaches its maximum size near mid gestation then rapidly decreases after birth. Actual regression of the thymus begins around puberty and the extent and speed in which it regresses will vary by husbandry practices and genetics.

The cells that initially infiltrate the thymus are of unknown origin, but thymic development and differentiation of thymocytes into specific CD cell lines occurs during gestation. Some of this development and differentiation can occur in secondary lymphoid organs as well. B cells, by contrast, develop and differentiate in the fetal bone marrow. There is a steady increase in the peripheral lymphocytes throughout gestation. The majority of these circulating fetal lymphocytes are T cells. At the same time that lymphocytes are developing in the fetus, development and expansion of other white blood cell populations is occurring.

The Neonatal Immune System

The immune system is fully developed, albeit immature, in the neonate. Susceptibility of the newborn to microbes is not due to any inherent inability to mount an immune response but is due to the fact that their immune system is unprimed[4]. Although there are higher numbers of phagocytic cells in the neonate, the function of these cells is decreased (these deficiencies are found, in calves, for up to four months of age)[5]. Complement is from 12-60% of adult levels at birth. Complement will not reach adult levels in calves until they are six months of age. There is a slow maturation of the immune system in mammals. As an animal approaches sexual maturity and begins to cycle the immune system also matures. In cattle, most of the immune system maturity is seen by 5-6 months of age. For example, T cells (CD4+, CD8+ and TCR$\gamma\delta$+) cells don't reach peak levels until the animal is eight months of age[6]. This doesn't mean a young calf can't respond to antigens but the response will be weaker, slower and easier to overcome. For all practical purposes, this immaturity leads to moderation of disease rather than prevents infection. Since in our food producing mammals the placenta is of the epitheliochorial type (cattle, pigs, sheep) there is no transplacental transfer of antibodies or white blood cells. Therefore an important component of the newborn food animal's defense mechanism is colostrum.

Colostrum

Colostrum is the most important example of passive immunity. Defined as the "first" secretions from the mammary gland present after giving birth, colostrum has many known and unknown properties and components. Constituents of colostrum include: concentrated levels of antibodies and many of the immune cells (B cells, CD cells, macrophages and neutrophils) and these cells are functional[7]. Immune system chemicals such as interferon[8];: and many nutrients are also in concentrated forms.[9]. The primary colostral antibody in most domestic species is immunoglobin class G except in ruminants in which the primary antibody of colostrum is IgG1. The function of the various cells of found in colostrum is still undergoing much research. The cells are know to enhance defense mechanisms in the newborn animal in the following ways: transfer of cell mediated immunity, enhanced passive transfer of immunoglobins, local bactericidal and phagocytic activity in the digestive tract and increased lymphocyte activity. Research in swine has shown higher absorption of these white blood cells when the sow is the true dam as compared to grafted piglets. Similar studies have not been done in ruminants. These cells are destroyed by freezing.

Colostrum Absorption

When any of our food producing mammals are born the cells that line the digestive tract allow absorption of colostral proteins via pinocytosis. As soon as the digestive tract is stimulated by ingestion of any material, the cells begin to change to cells that no longer permit absorption. By six hours after birth only approximately 50% of the absorptive

capacity remains by eight hours; 33% and by 24 hours; no absorption is available[10]. So colostrum transfer is a function of quality and quantity of the colostrum as well as the timing of colostral administration. In the Holstein breed, the first feeding should be a minimum of 3 quarts (3 liters) of colostrum. Also, colostrum high in red blood cells will make any scours caused by gram negative bacteria worse. Colostral supplements are available as well as products, both for oral or systemic administration, that contain specific antibodies. Although there is mixed feelings on their efficacy, in colostrum deprived animals they may have a significant value in decreasing mortality and/or severity of morbidity.

Maternal Antibody Interference Revisited

One of the accepted beliefs is the ability of maternal antibody to block immune responses from vaccination. This has been based on vaccination followed by a titer evaluation in the vaccinates. It is clear, from many studies, that animals vaccinated, in presence of high levels of maternal antibody to that antigen, may mot display increased antibody levels. However, recent studies have shown both the formation of B cell memory responses[11,12,13] as well as cell mediated immune responses in the face of maternal antibody[14] when attenuated vaccines were used. Similar responses have been reported in laboratory animals as well[15,16,17]. It is clear form these studies that maternal antibody interference of vaccines is not as absolute as once thought and the immune status of the animal, the specific antigen and presentation of that antigen should be considered when trying to design vaccination programs when maternal antibody may be present.

Impact of Stress

Stress impacts the neonate's immune system as it does older animals. Whether it impacts them more severely. There are several factors that can affect the immune system that is unique to the neonatal animal The birthing process has a dramatic impact on the newborn's immune system due to corticosteroid release. Furthermore the newborn has an increased number of Suppressor T cells. These factors, plus others dramatically decrease systemic immune responses for the first week of life. Systemic vaccinations during this time should be avoided due to these decreased responses and may even have undesired effects[18]. Other stresses should be avoided in the young calf to try and maintain immune system integrity in the immunologically frail newborn. Procedures such as castrations, dehorning, weaning and movement need to be considered as stresses in this animal and all have the potential to decrease immune system function temporarily.

Vaccination

As shown above the vaccination of the young calf is being revisited. Use of many different types of vaccines is routinely done in veal, dairy beef and dairy replacement heifers as well as branding/turnout vaccinations in beef calves Effectiveness of the

programs is an interaction of several factors: These include antigen (i.e. IBRV vs. *Pasteurella hemolytica*) and antigen (i.e. modified live or inactivated), age of the calf, for some antigens, presence of maternal antibody, other stress factors present at the time of vaccination and timing of disease agent exposure. Vaccines utilizes the mucousal immune system have been tested and licensed for use in the young calf, including the newborn. These vaccines include modified live, intranasal IBR/PI3 vaccines and modified live, oral rotavirus/coronavirus vaccine. Exact timing of early vaccination will vary somewhat by antigen and presentation. In human immunology times in which antigen exposure may cause a predominance of IgE have been shown. Similar immune responses have not been shown in food animals. However, our research has shown that initial systemic vaccination, for the four primary viral diseases (BVDV, IBRV, BRSV and PI3), has little impact when administered during the three week to five week of age window in dairy calves. This corresponds to the time frame in which maternal T cells are disappearing from the calf. However, if the calf is vaccinated before then, vaccination in that time seems to work well (i.e. a one week, five week of age vaccination program)[19,20]. In general, vaccination in the young calf should precede anticipated or historical times of disease by at least ten days, allowing the immune system to respond before exposure. If a booster dose is required then the boostered should be timed to be administered at least ten days before the expected problem time. Vaccination against diseases which have a primary cell mediated protective mechanism may be more likely to stimulate protection in the face of maternal antibody than those of which humoral immunity is the primary protective mechanism. Although in its infancy, the use of vaccination programs in young food animals is gaining popularity and more research is needed to further define protection and the timing required by different vaccines in the neonate.

Summary

The neonatal immune system is a complex and interrelated system containing components from both the dam and the newborn. Although the system is capable of responding and inferring varying degrees of protection, it is this combination of passive and active immunity together that provides protection, often in the form of decreased severity, to the neonate.

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