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# Neonatal Immunology

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## KEYWORDS

• Immunology • Neonatal • Calf • Vaccination • Development

The field of neonatal immunology continues to be an area of active research in human and veterinary medicine. New and advanced methods for assessing immune status and function are being used widely to re-evaluate some of the old beliefs about the young animal's immune system. Although much more research is still needed, 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.<sup>1</sup> The fetus does become immunocompetent while in utero to many diseases, however. In calves, this has been demonstrated with a wide variety of diseases.<sup>2-5</sup> 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 fetal lambs and calves between days 27 and 30 of gestation as an epithelial chord.<sup>6,7</sup> As a percentage of body weight, the thymus reaches its maximum size near midgestation and then rapidly decreases after birth. Actual regression of the thymus begins around puberty, and the extent and speed at which it regresses vary by husbandry practices and genetics. By the time of first heat cycle, the thymus' function as an immune gland is almost completely gone.

The cells that initially infiltrate the thymus are of unknown origin, but thymic development and differentiation of thymocytes into specific T cell lines occur 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.<sup>8</sup> Most 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 are occurring.

## NEONATAL IMMUNE SYSTEM

The immune system is fully developed, albeit immature, in the neonate at the time of birth. Susceptibility of newborns to pathogens is not attributable to any inherent

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inability to mount an immune response but is caused by the fact that their immune system is unprimed.<sup>9</sup> Although there are greater numbers of phagocytic cells in the neonate, the function of these cells is decreased (in calves, these deficiencies are found up to 4 months of age).<sup>10</sup> Complement is from 12% to 60% of adult levels at birth. Complement does not reach adult levels in calves until they are 6 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 to 8 months of age. For example, T cells (CD4+, CD8+ and TCR $\gamma\delta$ + cells) do not reach peak levels until the animal is 8 months of age.<sup>11</sup> This does not mean that a young calf cannot respond to antigens, but the response is weaker, slower, and easier to overcome. For all practical purposes, this immaturity may lead to moderation of disease rather than to complete prevention. Because the placenta is of the epitheliochorial type in food animal species (eg, cattle, pigs, sheep), there is no transplacental transfer of antibodies or white blood cells. Therefore, no discussion on bovine neonatal immunology is complete without a discussion on an important component of the newborn calf's defense mechanism, colostrum.

### COLOSTRUM

Colostrum is the most important example of passive immunity. Defined as the "first" secretions from the mammary gland present after birth, colostrum has many known and unknown properties and components. The information on the short- and long-term impacts of colostrum in calves continues to grow. Not only does good passive transfer have an impact on morbidity and mortality in the young calf,<sup>12-14</sup> but it has a positive impact on long-term health and production.<sup>15-17</sup> Constituents of colostrum include concentrated levels of antibodies and many of the immune cells (B cells, CD cells, macrophages, and neutrophils), which are fully functional after absorption by the calf.<sup>18</sup> Additional components of the immune system, such as interferon, are transferred by means of colostrum,<sup>19</sup> along with many important nutrients.<sup>20</sup> The primary colostrum antibody in most domestic species is IgG; in ruminants, this is further defined as IgG1. The functions of the various cells found in colostrum are still undergoing much research. The cells are known 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.<sup>12,21</sup> Research in swine has shown higher absorption of these white blood cells when the sow is the true dam as compared with grafted piglets. Similar studies have not been done in ruminants. These cells are destroyed by freezing and naturally disappear from the calf between 3 and 5 weeks of age.<sup>12</sup> The long-term impact of these cells on health or production of calves is not well understood at this time.

### COLOSTRUM ABSORPTION

When calves are born, the epithelial cells that line the digestive tract allow absorption of colostrum proteins by means of pinocytosis. As soon as the digestive tract is stimulated by ingestion of any material, this population of cells begins to change to those that no longer permit absorption. By 6 hours after birth, only approximately 50% of the absorptive capacity remains; by 8 hours, 33%; and by 24 hours, no absorption is typically seen.<sup>12</sup> Colostrum transfer is thus a function of quality and quantity of the colostrum in addition to the timing of colostrum administration. In the Holstein breed, the first feeding should be a minimum of 3 qt (3 L) and preferably 4 qt of

high-quality clean colostrum. Also, colostrum high in red blood cells may exacerbate any diarrhea caused by gram-negative bacteria.<sup>22</sup> In spite of all the information regarding the importance of colostrum administration to the calf, some degree of failure of passive transfer is common even in beef calves.<sup>13,23</sup> Colostral supplements are available, in addition to products for oral or systemic administration, that contain specific antibodies or general IgG concentrations. There is tremendous variability in the IgG concentration of colostral supplements.<sup>24</sup> Although mixed results pertaining to the efficacy of these products have been observed,<sup>25</sup> they may have significant value in decreasing the mortality or the severity of disease in colostrum-deprived calves.

#### VACCINATION TO IMPROVE COLOSTRAL QUALITY

It has long been thought that vaccines administered to a cow before calving increase colostral antibodies against those specific antigens. This has been best demonstrated with vaccines that are administered to cows against neonatal diarrhea pathogens. These vaccines are designed to increase the colostral antibody concentration against specific organisms that cause diarrhea in calves, such as *Escherichia coli*, rotavirus, and coronavirus.<sup>26–28</sup> Little research has been done looking at other vaccines and their impact on colostral antibodies, however. Although one study demonstrated that vaccinating cows with a modified-live viral vaccine increased colostral antibodies,<sup>29</sup> a recent study with inactivated viral vaccination of cows did not show the same response.<sup>30</sup> One Israeli study actually demonstrated decreased colostral antibodies when cows were vaccinated before calving.<sup>31</sup> If a vaccine is being designed primarily to improve colostral transfer of antibodies, studies should be requested that demonstrate the vaccine's ability to produce the desired effect.

#### MATERNAL ANTIBODY INTERFERENCE REVISITED

One of the commonly held beliefs in neonatal immunology is that the presence of maternal antibody blocks the immune responses associated with vaccination. This has been based on vaccinating animals, followed by evaluating subsequent levels of antibody titers. It is clear from many studies that if animals are vaccinated in the presence of high levels of maternal antibody to that antigen, they may not display increased antibody titers after vaccination.<sup>32,33</sup> Nevertheless, recent studies have shown the formation of B-cell memory responses<sup>34–36</sup> and cell-mediated immune responses in the face of maternal antibody<sup>28</sup> when attenuated vaccines were used. Similar responses have been reported in laboratory animals as well.<sup>37–39</sup> It is clear from these studies that maternal antibody interference of vaccines is not as absolute as once thought. The immune status of the animal, particularly against that antigen; the specific antigen; and presentation of that antigen should be considered when trying to design vaccination programs when maternal antibody may be present. In summary, work published to date (and cited previously) has demonstrated that vaccination against diseases that have a primary cell-mediated protective mechanism may be more likely to stimulate an immune response in the face of maternal antibody than those in which humoral immunity is the primary protective mechanism (**Table 1**).

#### IMPACT OF STRESS

Stress has an impact on the calf's immune system as it does in older animals. There are several factors that can affect the immune system and are unique to the neonatal animal. The calving process has a dramatic impact on the newborn's immune system because of corticosteroid release. Furthermore, the newborn has an increased

| Table 1<br>Diseases with research that has assessed maternal antibody interference in cattle |   |
|--|---|
| Primarily Cell-Mediated Protection:<br>Vaccination not Blocked by Maternal<br>Antibody       | Primary Antibody Protection:<br>Vaccination Blocked by Maternal<br>Antibody |
| BRSV   | Bovine viral diarrhea   |
| BHV-1  | <i>Mannheimia haemolytica</i>   |
| Parainfluenza virus  | <i>Pasteurella multocida</i>  |
| <i>Leptospira borgpetersenii</i>   | —   |
| Pseudorabies   | —   |

number of suppressor T cells. These factors, along with others, dramatically decrease systemic immune responses for the first week of life. Recent research has demonstrated that there is actually a decrease in the immune response of neonatal calves. From birth, there is a decrease in immune responses until day 3, when they are at their lowest levels (Fig. 1).<sup>40</sup> By day 5, these responses are back to the level of immune responses seen on the day of birth. Systemically administered vaccinations during this time should be avoided because of these decreased responses. Vaccination immediately after birth may even have undesired effects.<sup>41</sup> Furthermore, other stresses should be avoided in the young calf to try and maintain immune system integrity in the immunologically frail newborn. Procedures like castration, dehorning, weaning, and movement need to be considered as stresses that have the potential to decrease immune system function temporarily.

## VACCINATION

As discussed previously, the vaccination of the young calf is being revisited. Many different types of vaccines are routinely used in veal, dairy beef, and dairy replacement heifers in addition to branding/turnout vaccinations in beef calves. The effectiveness of these programs is attributable to an interaction among several factors, including antigen (ie, infectious bovine rhinotracheitis [IBR] versus *Pasteurella haemolytica*) and vaccine type (ie, modified-live or inactivated), age of the calf, presence of maternal

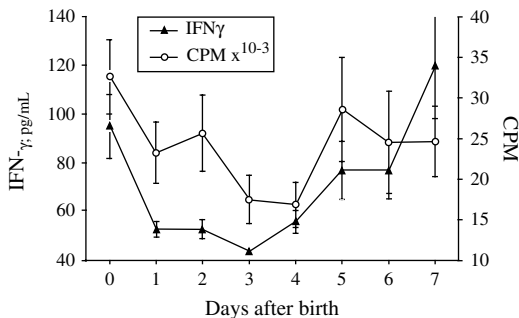


Fig. 1. Graph illustrates the immune dysfunction present in the neonatal calf and shows diminished cytokine (interferon- $\gamma$  [IFN $\gamma$ ]) production and blastogenic responses in the first few days after birth. CPM, counts per minute. (Data from Marcus Kehrl, DVM, PhD, Ames, IA.)

antibody, other stress factors present at the time of vaccination, and timing of disease agent exposure. Vaccines that use the mucosal immune system have been tested and licensed for use in the young calf, including the newborn. These vaccines include modified-live vaccines; intranasal IBR/PI3 vaccines; modified-live vaccines; oral rotavirus/coronavirus vaccines; and new intranasal vaccines containing bovine viral diarrhea virus (BVDV) types 1 and 2, bovine herpesvirus (BHV)-1, PI3 and bovine respiratory syncytial virus (BRSV), or BRSV in combination with PI3. For BRSV in which limited replication occurs with systemic modified-live vaccination, intranasal administration may be the most effective route.<sup>42</sup> Exact timing of early vaccination varies somewhat depending on antigen and presentation. In human immunology, times during which antigen exposure may cause a predominance of IgE production have been shown. Similar immune responses have not been demonstrated in food animals. One study has shown that initial systemic vaccination for the four primary viral diseases (BVDV, infectious bovine rhinotracheitis [IBRV], BRSV, and PI3) has little impact when administered during the 3-week-old to 5-week-old age window in dairy calves, however.<sup>42</sup> The author's own work has seen the same problems with vaccination during this time. This corresponds to the time frame in which maternal T cells are disappearing from the calf.<sup>18,21</sup> Several other studies have looked at vaccinating calves before 3 weeks of age, with good response.<sup>28,43,44</sup> In general, vaccination in the young calf should precede anticipated or historical times of disease by at least 10 days, allowing the immune system to respond before exposure. If a booster dose is required, the booster should be given at least 10 days before the expected disease occurrence. Although in its infancy, the use of vaccination programs in young food animals is gaining popularity and more research is needed to define protection and the timing required by different vaccines in the neonate further.

## SUMMARY

The neonatal immune system is a complex and interrelated system containing components from 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 to the neonate.

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