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IMMUNITY IN THE CALF

Amelia R. Woolums, DVM MVSc PhD DACVIM DACVM
University of Georgia Department of Large Animal Medicine
Athens, GA 30602

INTRODUCTION

The neonatal calf is born into an environment populated by bacteria, viruses, and parasites with the capacity to overtake the calf's body and end the calf's life. In order to resist invasion by these infectious agents, the calf has a system of immunity that is capable of recognizing and eliminating thousands of different pathogens, while limiting damage to the host. However, the immune response is immature and "uneducated" in early life, and must learn though interaction with infectious agents. Assistance during this naïve phase of immunity comes from factors absorbed from the dam's colostrum. As the calf grows, its interactions with pathogens through vaccination or natural infection lead to a mature immune response capable of protecting the adult cow from numerous diseases, and allowing her to produce colostrum that protects her calves from disease.

IMMUNE DEVELOPMENT IN THE CALF

Prenatal immunity

The immune response begins developing while the calf is *in utero*. For example, the thymus, which is the site of T lymphocyte development, is evident by 40 days of gestation, and fetal calves are able to mount an immune response to certain viruses as early as 73 days of gestation. The ability of the immune system to respond to infection gradually broadens as gestation progresses, although in the days immediately preceding birth many functions diminish because of the immunosuppressive effect of steroid hormones in the fetus and dam. If a calf is infected *in utero* by an agent which does not kill the fetus and/or cause abortion, measurable levels of antibody to the agent can be found in the serum of the newborn calf at birth, before it nurses colostrum.

Immunity in the neonatal calf

Passive antibody acquisition from colostrum: Unless a calf is infected *in utero*, at birth the calf has no significant levels of antibody in plasma or on body surfaces. Levels of soluble factors involved in the immune response, such as proteins of the complement system, are also lower in the neonatal calf than in adult cattle. Moreover, cells of both the innate and acquired arms of the immune response have diminished function in the newborn calf, and cells of the acquired immune response have not yet been "educated" by exposure to vaccines or infections. Thus, the newborn calf is exquisitely sensitive to infection. A solution to this problem is provided in the form of colostrum from the dam. Colostrum, which is produced in the cow's mammary gland in the final weeks of gestation, contains a very high level of antibodies to any pathogen the cow has previously been exposed to. In the first few days of life, the calf's intestinal cells take up proteins whole and intact (rather than digesting them into component amino acids, as will be the case after the calf is a few days old). Thus, antibody molecules in colostrum are taken up intact into the plasma, where they circulate for months, providing the calf with protection against infectious agents it encounters. Moreover, colostral antibody also provides protection on the surface of the

intestine (and can be secreted from the plasma back into the intestine), providing the calf with protection against intestinal infections that can cause diarrhea and death. The critical nature of colostrum in the health of the neonatal calf has been proven by repeated studies which show that calves that fail to obtain adequate colostrum are much more likely to develop disease and to die, or to fail to grow and produce at their expected rate, as compared to calves with obtain adequate amounts of colostrum.

In addition to antibodies, colostrum provides calves with a large dose of fat soluble vitamins, which are otherwise low in newborn calves. Fat soluble vitamins, such as vitamin A, D, and E, are necessary for a variety of responses by immune cells. Soluble factors such as lactoferrin in colostrum also appear to influence the neonatal immune response.

Importance of maternal cells in colostrum: While the importance of colostrum in transferring antibody to calves is well known, recent research has shown that maternal lymphocytes which are present in colostrum are also absorbed (or migrate) across the intestine of calves and enter the tissues, where they influence immune development. Researchers have shown that calves fed colostrum containing maternal cells developed the ability to stimulate an immune response faster than calves fed colostrum with maternal cells removed.[8] Moreover, immune responses to the viral pathogen bovine viral diarrhea virus (BVDV) could be identified in calves at one day of age when they were fed colostrum containing maternal cells, but not in calves fed colostrum without maternal cells.[2]

This and related research indicates that the cells in colostrum, as well as antibody, have an effect on calf immune development. The significance of this finding is not yet entirely clear, but it may indicate that efforts to provide calves with fresh (cell containing) colostrum, as opposed to frozen or fermented colostrum, may be worthwhile in terms of optimizing calf immune development. Pasteurization also kills cells in colostrum. However, until more is known about the importance of colostral cells in the immune development of the calf, because provision of good quality (high antibody titer, low bacterial count) colostrum is known to be necessary to ensure calf immunity, at this time it is still recommended to give frozen or pasteurized good quality colostrum, if fresh good quality colostrum is not available.

Development of acquired immune responses in neonatal calves: Significant changes in the components of the acquired immune response occur in the first few weeks of calf life. At birth, calves have higher numbers of γδ T cells and neutrophils circulating in the blood, as compared to adults, and lower numbers of B cells (reviewed in Chase et al.). In spite of these differences, calves can mount an immune response to an infection in the first few days of life, although these responses will not be as strong or effective as those in an adult animal. It is most accurate to think of the immune response of the newborn calf as functional, but immature and naïve. If calves have high levels of antibody passively acquired through colostrum ingestion, acquired immune responses in the first month or more of life will be blunted, because maternal antibodies provide negative feedback to the calf's immune response, suppressing further antibody production. Interestingly, recent research has shown that, while vaccination of calves with moderate levels of antibody from colostrum will not induce calves to produce more antibody, T cells in vaccinated calves are nonetheless stimulated, and able to mount a memory-type response when they are re-exposed at a later date to the infectious agent contained in the vaccine.

Immune responses in neonatal animals are noteworthy for being relatively biased toward a "T helper type 2" response. This means that the neonatal calf immune response is more effective at producing antibody than it is at activating responses effective against intracellular infections, such as those by viruses and bacteria such as the agent that causes Johne's disease. Thus calves have relatively diminished capability to develop protective immunity against viruses and intracellular bacteria, and vaccines against these agents may be less effective in neonatal calves than they are in older calves or adults.

Effect of nutrition on neonatal immunity: Adequate nutrition is well known to be necessary for adequate immune responses to occur in cattle. In general, supplementing diets that are deficient in protein, energy, vitamins, or minerals has been shown to improve immune responses to vaccination and other stimulation. However, treatment of cattle with vitamins and minerals in excess of required levels does not always improve the immune response (reviewed in Galyean et al.). With specific reference to neonatal calves, newborn Holstein calves fed at 50% of maintenance requirements for protein and energy for the first month of life had decreased lymphocyte responses and decreased ability to produce antibody following vaccination, as compared to calves fed maintenance requirements.[6] Because these investigators fed calves 50% of their requirement of milk replacer but did not correct for deficiencies of vitamins and minerals that may have occurred in underfed calves, vitamin and mineral deficiency may have also impacted immune responses in the calves in this study. In other research, lymphocytes from calves fed an intensified milk replacer (30% crude protein and 20% fat, fed at 2.5% of body weight on a dry matter basis per day) produced less interferon gamma and more nitric oxide following stimulation, as compared to calves fed a standard milk replacer diet (20% crude protein and 20% fat fed at 1.4% body weight of dry matter per day).[7] As calves aged, lymphocytes from calves fed an intensified milk replacer diet did not respond to stimulation to the same degree as calves fed a standard milk replacer.[4] The importance in these differences is not yet clear, but the research does indicate that intensified milk replacer feeding has an effect on immune responses in calves on these diets.

Vaccination of calves: For decades, veterinary students and cattle producers have been taught that neonatal calves cannot respond to vaccination because of the blocking effects of maternal antibody. However, research has shown that, in at least some cases, young animals vaccinated in the face of maternal antibody, while not showing evidence of an increase in serum antibody levels typically seen in older animals responding to vaccination, will show evidence of T cell activation or, more importantly, protection from disease when they are exposed to infection after maternal antibodies have disappeared. In general, successful vaccination of calves with moderate levels of maternal antibody requires two doses of vaccine given at least 2-4 weeks apart, but exceptions to this rule have been identified. However, these findings are not consistent; occasionally young animals vaccinated in the face of maternal antibody fail to develop a protective immune response to later challenge.

The reasons that calves are often but not always successfully protected when vaccinated in the face of maternal antibody are not completely defined, but they are likely related to the following factors:

age of the animal at vaccination
the concentration maternal antibody present at vaccination
the type of vaccine given to the calf

the number of doses of vaccine given to the calf
the route by which the vaccine is given
the virulence of the challenging pathogen
the outcome used to define success of vaccination.

While more research is needed before perfect recommendations for successful vaccination of calves with maternal antibody can be made, ample evidence suggests that, in at least some cases, vaccination calves with maternal antibodies can help protect them from disease.[10] See the "take-home points" below for some general recommendations regarding vaccination of calves with maternal antibodies.

KEY TAKE-HOME POINTS

1. While the neonatal calf has an immune system capable of responding to infection or vaccination, it is naïve and immature, compared to the adult immune system. Intake of adequate amounts of colostrum at birth is essential to protect calves from infection while their immune response is maturing and developing the capacity to respond to infection.

2. Research indicates that maternal cells in colostrum move across the intestinal wall of calves and enter their tissues, where they seem to influence the development neonatal immune responses. The importance of this finding is that frozen or pasteurized colostrum and colostrum replacers do not contain whole functional cells and thus may not stimulate the same type of response as that stimulated by fresh colostrum containing whole cells. However, more research is necessary to determine the practical importance of this difference. While it is ideal to feed fresh high quality (high antibody concentration and low bacterial count) colostrum, at this time it is still recommended to feed high quality frozen colostrum if high quality fresh colostrum is not available.

3. Feeding "intensified" diets to calves increases some immune responses and decreases others, as compared to responses in calves fed traditional milk replacer diets. More research is necessary to determine how these effects impact calf health.

4. While veterinarians and producers have traditionally understood that calves cannot be vaccinated effectively while they have circulating levels of maternal antibodies from colostrum, recent research indicates that calves vaccinated in the face of maternal antibody can sometimes mount T cell responses to vaccination, and may have improved protection against disease when maternal antibodies have disappeared. This is true even when calves do not seroconvert following vaccination in the face of maternal antibodies.

When developing plans to vaccinate calves with circulating maternal antibody, keep in mind the following:

a. calves are more likely than adults to require booster vaccinations, which should be given at least 2 to 4 weeks after the initial vaccination;
b. intranasal vaccines may be more effective than injected vaccines in calves with moderate to high concentrations of maternal antibodies; however, immunity from intranasal vaccines may not last more than a few months;[3,9]

c. repeated doses of intranasal vaccines may not boost as effectively as repeated doses of injected vaccines;
d. calves with very high concentrations of maternal antibody--such as those found in the first month of life in calves with good passive transfer –may not respond as well to vaccination as calves with moderate to low concentrations of antibody;
e. vaccines should be administered so that the final dose is given no later than 1-2 weeks before the expected exposure of the group to infectious agents.

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