Transition diseases and the immune system
By Geni Wren | 3/1/2007

Editor’s note: First in a two-part transition immunology series.

Once a dairy cow calves, trying to bolster her immune system at that point is an exercise in futility. Immune changes relative to uterine problems start one to two weeks prepurum. If the immune system has gone into a downward spiral, that can set her up for retained placenta (RP), metritis and endometritis. Preventing metabolic diseases pre-calving with proper nutrition to “feed” the immune system can go a long way in reducing these problems, but careful attention to management needs to take place.

Jesse Goff, DVM, PhD, of the USDA’s National Animal Disease Center, Ames, Iowa, says metabolic disease of the dairy cow is strongly associated with decreased fertility and also can have a tremendous negative effect on the immune system. A strong immune system is also required if immune recognition of a conceptus is to occur so that implantation can proceed.

The cow’s system is designed to allocate her resources to milk production, even at the expense of her immune system. Neutrophil and lymphocyte function is diminished in the periparturient period, especially in the dairy cow. “If the cow did not make quite as much milk, she would theoretically be in better balance for energy and protein, allowing better immune cell function,” Goff says.

“All cows suffer some immune suppression, at least in the last week prepartum and the first week after calving,” adds Stephen LeBlanc, DVM, DVSc, University of Guelph. “Cows at risk of RP, metritis, etc. have more severe suppression, which generally starts earlier.”

MILK FEVER AND THE IMMUNE SYSTEM
Occasionally, hypocalcemia, or milk fever, occurs just before calving or in mid-lactation, but the great majority of cases are within 24 hours of calving. Milk fever increases susceptibility to infection by removing some of the physical barriers to infection, such as failure to close the teat end completely after milking so bacteria have access to the mammary gland.

Goff’s research demonstrates that the ability of the immune cells to respond to bacterial infection is directly reduced by low blood calcium. Typically, when a neutrophil, the first line of defense against bacterial infection, encounters a bacterial cell wall or other bacterial product, it triggers a response within that cell. Goff explains that the response is an increase in intracellular free calcium concentration, which activates a variety of enzymes and cell pathways aimed at destroying bacterial invaders.

The source of that rise in intracellular free calcium is calcium stored within organelles, such as the endoplasmic reticulum of the cell. “Unfortunately, with low blood calcium in the cow, the intracellular calcium stores are slowly depleted,” he says. This means the ability of the cells to respond to stimuli is blunted. “This is why it is so critical to use strategies such as manipulating dietary cation-anion balance to maintain normal blood calcium concentration,” Goff notes.

“I also think that if we look at these problems “upstream,” some of the same risk factors, such as not eating well, contribute to both hypocalcemia and immuno function/uterine disease, even though their final mechanistic pathways are different,” LeBlanc adds.

Milk fever cows also are in a stressed condition. This causes them to secrete large amounts of cortisol, a highly immune-suppressive hormone.

EFFECT OF KETOSIS ON IMMUNITY
Ketosis in this country, with confined herds fed a total mixed ration, usually shows up between five and 10 days after calving. Classical clinical ketosis, as described for grazing cows, takes a little longer to develop -- maybe 10 to 20 days in milk. For less intensively managed cattle, the window is probably about 15 to 45 days in milk.

During ketosis a cow has trouble maintaining adequate glucose levels in the blood and is mobilizing a lot of body fat. “Like most cells of the body, immune cells need fuel to operate, and when glucose is low, they do not have the energy needed to function properly,” Goff says. “They do not use the ketone bodies derived from fat very well for energy. They do use glutamine -- an amino acid derived from muscle proteins -- quite well for energy, but glutamine is also being used in place of glucose by other cells of the body and is in short supply.”

Though not well-defined for the cow, a rise in NEFA -- non-esterified fatty acids in the blood -- during ketosis may have its own direct negative effects on immune cell function.

Left displaced abomasum is usually seen in the first 10 days after calving. The cow with a displaced abomasum has serious problems with energy balance. “As little to no nutrients are getting to the small intestine, protein balance is also going to be affected,” Goff says. “Without the fuel and the building blocks to produce new cells and antibodies, it is common for the DA cow to develop all kinds of secondary problems, such as metritis and mastitis.”

All of this leads to the current dilemma: “As the amount of grain and starch in a diet increases pre-calving, we saw increased intakes in the minus-three to minus-one week pre-calving period,” Goff says. “But as we enter the immediate pre-calving period on these diets, we see a good percentage of cows suffer a rather dramatic fall in feed intake, which may be precipitating some of our metabolic (ketosis and fatty liver) problems. So in the end, simply promoting greater feed intake in the close-up period, without considering the last few days of the dry period as critical, may have put us into the situation where many are opting for the high straw pre-calving diets.”

Goff adds that, in this period, avoiding pen changes and social stresses as much as possible is a good idea.

Once cows are off feed and are sick, Goff’s strategy is to greatly increase the amount of hay and dry grain mix and decrease fermented hay and corn silages for a while. “This seems to suit the sick cow better.”

And don’t forget about water during this time. It has been well-documented that there are problems with unclean water high in bacteria causing the immune system to work overtime to handle the bacterial load. “This cuts the amount of energy left to make milk, and switching to clean water or at least treating the water often gets good results,” Goff suggests.

IMMUNITY AND RETAINED PLACENTA (RP)
Studies by Gunnick (1984) suggested the fetal placenta must be recognized as “foreign” tissue and rejected by the immune system after parturition to cause expulsion of the placenta. Retained placenta is failure to pass the placenta within 24 hours after parturition. Neutrophils may play a key role in breaking down the placental attachment. Goff’s studies showed that neutrophils isolated from blood of cows with RP had significantly lower neutrophil function...
prior to calving, and this impaired function lasted for one to two weeks after parturition.

“These data suggest neutrophil function determines whether or not the cow will develop RP,” Goff says. “They also suggest that depressed production of interleukin-8 may be a factor affecting neutrophil function in cows developing RP.”

According to LeBlanc, animals with elevated NEFA levels (NEFA ≥ 0.5 mEq/L) and/or suboptimal vitamin E status in the last week prepartum are more likely to have RP. Cows with RP are more susceptible to mastitis, and though RP probably does not cause mastitis, it is symptomatic of a depressed immune system. RP is also a substantial risk factor for metritis and endometritis.

Optimal nutrition is very important for prevention of RP, especially in the last one to two weeks pre-calving, and probably longer, LeBlanc says. “Immune function requires many inputs, such as energy, protein, antioxidants, etc., so feed intake in general is important, and is a good barometer of how well management is succeeding in decreasing the risk of RP and other transition diseases.”

The periparturient period may represent a period of increased oxidative stress to the cow. Antioxidant supplementation has been shown to enhance neutrophil function and contribute to prevention of RP and mastitis. The two biggest contributors are vitamin E and selenium. Research shows that up to 2000 IU/day of dietary vitamin E may reduce the incidence of RP, even in cows receiving the legal limit of 0.3 ppm Se.

“While there may be some benefit to higher levels of vitamin E supplementation for mastitis, I’m not aware of any data that going higher than 2000 IU/d reduces RP under normal conditions,” LeBlanc explains. “Immune function in general, and RP in particular, is multifactorial, so it’s not reasonable to expect any one nutrient to be the silver bullet.”

A field study by LeBlanc in the last few years found that injection of 3000 IU of vitamin E one week before expected calving reduced the risk of RP by half, but only in those cows with suboptimal vitamin status (measured in serum) pre-treatment. This was about one-third of the more than 1,100 cows in the study; in the majority, it made no difference. “We found a great deal of variability in vitamin E status both between herds and among animals within a herd,” LeBlanc says.

There is no easy or inexpensive way to estimate whether individuals or herds will benefit from injection of vitamin E. However, a follow-up study by LeBlanc showed that blood and neutrophil levels of vitamin E are increased for five to seven days after injection, so if cows are to be injected, one week before due date is the time to do it, he advises. Conversely, after injection of selenium, blood levels are increased for about a month. This small study found no difference in the rate or peak of vitamin E absorption when injected subcutaneously or intramuscularly.

Research from The Ohio State University over a decade ago identified optimal levels of Se for cell phagocytosis in the context of mastitis. “It is difficult, if not impossible, to maintain these levels around calving, while respecting the legal limit of dietary Se supplementation,” LeBlanc states. “The transition period may be a niche for organic Se to get greater absorption from the same amount of Se.”

LeBlanc cautions, however, that with injectable Se, the difference between supplementation and toxicity is only one decimal place.

**METRITIS AND ENDOMETRITIS**

Metritis is caused by a large number of bacteria growing unchecked in the uterus. It results in a foul-smelling, red-brown watery discharge from the uterus and systemic signs of sickness within 10 to 14 days after calving. Work by Hammon, et al (2006) showed that neutrophils of cows with metritis are significantly less able to kill bacteria than neutrophils from cows without metritis. “The surprise in these studies was that poor neutrophil function was evident in these cows the day of calving -- before lactation began and before any bacteria could have entered the uterus,” Goff says.

Endometritis is inflammation of the lining of the uterus -- without systemic signs -- lasting more than three to four weeks after calving. Hammon showed that cows with endometritis and subclinical endometritis had poorer neutrophil function than cows with a healthy uterus.

The principle for prevention of transition diseases is to optimize peripartum immune function, principally through management, to encourage feed intake in the transition period, LeBlanc says. “All of these diseases are multifactorial and no one preventive measure will be universally effective.”